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13. ABSTRACT (Maximum 200 Words) The purpose of this project is to refine a "visual neural network," coupled to a mammographic database, and evaluate the ability of the resulting system to help radiologists reduce the number of benign biopsies in mammographic screening without increasing the number of missed cancers. We refer to this as a "mapped database diagnostic system." The unique features of this system are a) its exploitation of a clinically proved database of mammograms for enhanced diagnosis, b) automatic selection of highly discriminating mammographic features, and c) a two-dimensional "relational map" for enhanced browsing through the mammographic database. Years 1 and 2 of this project will be devoted primarily to retrospective studies, Years 3 and 4 primarily to clinical studies. In Year 2, reported here, we acquired a database of biopsy-proven mammographic cases from UCLA and the King Drew Medical Center. In addition we developed new algorithms and software for classifying masses, we constructed and tested a new content-based image search engine for database-aided diagnosis and teleradiology, we constructed a radiologist-friendly interface for interacting with our database-aided diagnostic system, and we initiated the construction and testing of a telemammography system linking the Humphrey Comprehensive Health Center to our database-aided diagnostic system at the King/Drew Medical Center.			
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INTRODUCTION

The purpose of this project is to refine a "visual neural network," combined with a mammographic database, and test it for its ability to help radiologists reduce the number of benign biopsies in mammographic screening without increasing the number of missed cancers. We refer to this as a "mapped database diagnostic system." The unique features of this system are a) its exploitation of a clinically proved database of mammograms for enhanced diagnosis, b) automatic selection of highly discriminating mammographic features, and c) a two-dimensional "relational map" for enhanced browsing through the mammographic database.

Year 1 of this project was devoted primarily to retrospective studies and to preliminary development of the mapped database diagnostic system. A major effort in Year 2 was devoted to the design and implementation of a computer architecture of a full-service computer-aided diagnostic system. Our objectives in this design included ease of data acquisition and recording, sophisticated image manipulation, remote and local database-aided diagnosis, and semiautomated reporting. We believe these features of the design will encourage radiologists to use the diagnostic system, and will make the system transparent in testing our algorithms for computer-aided diagnosis. Years 3 and 4 will be devoted primarily to clinical studies.

Additional effort in Year 2 was devoted to improving our underlying detection and classification algorithms, improving our algorithms for finding and retrieving images that are similar the images under study, and integrating our algorithms for classifying masses and microcalcifications.

Another major effort in Year 2 was devoted to acquiring a statistically significant database of biopsy-proven mammograms. This work included the negotiation of data-sharing agreements with UCLA and the Humphrey Comprehensive Health Center, applying to the Institutional Review Boards at UCLA and KDMC for permission to carry out research involving human subjects, scanning and digitizing films, checking the accuracy of the data, and entering the data in our database.

BODY

The following are the tasks approved for our project for Year 2, along with the work that was carried out in Year 2 for these tasks.

Task 3. Collect and organize a database of proven mammographic regions of interest (months 1-6, 12-24)

- a. Collect film mammograms from at least 400 subjects, restricting the lesions to microcalcifications and masses. (The masses will include stellate lesions.) Add teaching files if possible. Include films from King-Drew Medical Center (KDMC) and from University of California at Los Angeles (UCLA). (months 1-2)
- b. Digitize all films on Lumiscan 85 film scanner at a 50-micron pixel width. Save all digitized mammograms on compact disc. (month 2)
- c. On each mammogram find one or more lesions, using the advanced lesion detector of Task 2. Enclose one or more of these lesions in a 512X512-pixel or a 1024X1024 – pixel square. We refer to this square as a region of interest (ROI). (months 3-4)

- d. Print hard copies of all of the digitized ROIs collected in Task 3c. Each radiologist on this project will partition the ROIs into groups of medically and perceptually similar ROIs. Each group will be identified by a medically or visually descriptive label. We refer to these as *perceptual similarity groups*. The radiologists will form a consensus on a final grouping and labeling of these groups. (month 5)
- e. Each radiologist will construct a dissimilarity matrix for these groups. Each element of this matrix will contain the radiologist's subjective estimate of the dissimilarity of the corresponding two groups on a scale from 0 to 5, 0 designating identity, and 5 designating extreme dissimilarity. (month 5)
- f. Label the resulting ROI as one of {mass, calcification, asymmetry, architectural distortion} and as one of {benign, malignant}. (month 5)
- g. Partition the database of ROIs into D and T , in a manner so that the distributions of types of abnormalities and perceptual similarity groups in D and T are similar. (month 6)
- h. Expand the collection of digitized film mammograms to 500 subjects, primarily from KDMC and UCLA. Include asymmetries and architectural distortions in addition to the microcalcifications and masses. Search for and collect mammograms containing screening errors associated with interval cancers, as well as mammograms containing minimal signs that preceded the observation of interval cancers. Search and collect mammograms with minimal signs that did not precede the observation of an interval cancer. Repeat the subtasks b to g. (months 12-18)
- i. Explore the possibility of collaborating with other institutions in the sharing of mammograms and other medical data related to the early detection of breast cancer. With this collaboration and continued acquisitions of proven mammograms from UCLA and KDMC, expand the collection of digitized mammograms to 1000 or more. Include as many as possible mammograms each of which contains an early sign of a cancerous lesion that was missed or misdiagnosed on that mammogram. (months 19-24)

RESEARCH ACCOMPLISHMENTS FOR TASK 3:

We acquired and organized a database of biopsy-proven mammographic cases from 35 patients at the King/Drew Medical Center (KDMC) and 280 cases at the University of California at Los Angeles (UCLA). The cases at UCLA covered patients observed during January 1998 to August 1999. Of these cases 120 were malignant, 20 were high risk benign, and 140 were benign. The cases at KDMC covered patients observed during January 2000 to May 2000. Of these cases 3 were malignant, 2 were high risk benign, and 30 were benign.

These cases are a significant expansion of our earlier database, which was restricted to a single region of interest for each case. Every candidate case for the new database was classified by the radiologist in accordance with the BIRADS categories of 0, 1, 2, 3, 4, or 5. Only the cases receiving BIRADS scores of 4 or 5 were sent to biopsy. Each of these biopsied cases was entered into our database, provided the full set of mammograms was found in the case's film jacket. Consequently all of the cases in the acquired database are diagnostic rather than screening. Each of these cases was scanned and digitized on our Lumiscan 85 scanner-digitizer, and entered into our computer system. Every case included at least two x-ray views of each breast (CC and MLO). In addition many of the cases included supplemental images such as

MRI, ultrasound and nuclear images (typically with technetium 99 tracers). Every case included the outcomes of biopsies. A primary or secondary physician requesting a mammographic study referred most of these cases to UCLA or KDMC.

Among the 35 cases from KDMC, biopsies indicated that 3 were malignant, 2 were high-risk benign, and 30 were benign. Among the 280 cases from UCLA, biopsies indicated that 120 were malignant, 20 were high-risk benign, and 140 were benign.

Every case in the database included films from earlier years. Thus the 123 malignant cases contain films in which the cancers were missed. These cases will enable us to carry out a retrospective study that will include an evaluation of the ability of our diagnostic system to reduce both the number of missed cancers as well as the number of unnecessary biopsies.

For the reporting of these cases we designed and used an expansion of the "mammography assessment and findings" form described in Addendum H of our proposal. We also adopted a list of acronyms ("pathology codes") to represent the observed pathologies, both benign and malignant. The expanded assessment form and the list of pathology codes are presented in Appendix 3.

The data in these cases are stored in three sections. The first section holds the patient medical information, such as age, history of breast cancer, incidence of cancer in close relatives, and the use of hormones. The second section contains the digitized mammograms and the regions of interest (ROIs). The third section contains information that describes the images, such as the sizes of the images, the size of the pixel, and the locations of the ROIs in the full mammogram.

In accordance with part *i* of this Task, we established a collaboration with the Hubert H. Humphrey Comprehensive Health Center (Humphrey Center, for short), using telemammography as a means of acquiring additional mammographic screening data and to facilitate carrying out the planned prospective tests for evaluating the effectiveness of our database-aided diagnostic system. The Humphrey Center receives many more mammographic screening cases than the King/Drew Medical Center – thereby providing a good population for evaluating the effectiveness of our database-aided screening system in reducing the number of unnecessary surgical biopsies without increasing the number of missed cancers. This collaboration is supported by a grant from the California Telehealth and Telemedicine System.

Task 4. Construct a graphical user interface for interacting with the two-monitor high-resolution display and the control monitor. This graphical user interface will be an expansion and refinement of the one-monitor interface shown in the proposal. Include a high-resolution simulated square magnifying glass that shows a window excised from the 4000×5000 -pixel array produced by the scanner. Include a brightness inversion capability. Include a brightness control and a contrast control. (months 14-15)

RESEARCH ACCOMPLISHMENTS FOR TASK 4:

We refined and expanded the capabilities of our graphical user interface. These refinements and expansions included new commands for the control monitor and for the high-resolution

monitor. The new commands for the control monitor consisted of a) patient data entry, b) image scanning, c) computer-aided diagnosis, and d) computer-aided clinical reporting. The new commands for the high-resolution monitor included a) magnification, b) inversion, c) brightness control, d) contrast control, e) panning, f) ROI selection, g) zooming, and h) selection of views among RMLO, RCC, LMLO, and LCC.

Task 5. Construct and train a visual neural classifier and a relational map. (months 16-17)

- a. Extract the set of features F_2 from the design set D . Use the genetic algorithm G_2 to find a set of reduced-dimensionality features for analyzing the ROIs. Using these reduced-dimensionality features for design set D , construct a database K of labeled reduced-dimensionality feature vectors for training the visual neural classifier. (month 16)
- b. Construct an initial 5-layer visual neural network and a relational map, based on the design principles described in [18-20]. (month 17)
- c. Train this neural network using the design set K to preserve perceptual similarity grouping and benign-malignant separation in the relational map. (month 17)

RESEARCH ACCOMPLISHMENTS FOR TASK 5:

Classification and detection of masses and microcalcifications require the abnormality to be separated from the background. This process is called “segmentation.” During Year 2 we designed and implemented a new, substantially improved segmentation algorithm. Continuing efforts in this area include the use of genetic algorithms to optimize the selection of the design parameters of “active contour models” for the segmentation of masses.

Our content-based image retrieval (CBIR) algorithm relies on a neural network that learns “perceptual similarity” as determined by a radiologist. During Year 2 we enhanced this algorithm by including a mutual information component that provides a more stable visual representation of the database. Currently the algorithm uses a single view of a lesion as an input to the algorithm. We are investigating the possibility of using two views of the breast as an input to the algorithm.

A major property of our diagnostic system is its ability to detect and classify masses and microcalcifications. This requires the integration of four principal algorithms: mass detection, mass classification, microcalcification detection, and microcalcification classification. Each of these principal algorithms consists of several constituent algorithms. The constituent algorithms include algorithms for preprocessing, feature extraction, and classification.

During the past year we designed, built, and carried out preliminary tests of an “application server.” The application server contains the system algorithms, including preprocessing, feature extraction, detection, and classification. The application server provides a framework for integrating the classifiers of microcalcifications and masses. The framework is sufficiently general to admit the integration of additional classifiers and imaging technologies, and for the refinement of individual algorithms without affecting the other algorithms. In addition the framework enables the radiologist to use the algorithms individually or in combination as a single system.

Task 6. Construct a neurodatabase system, consisting of the graphical user interface, the relational map, the visual neural classifier, and the database K. (month 17)

RESEARCH ACCOMPLISHMENTS FOR TASK 6:

We constructed a graphical user interface and a computer architecture that will work effectively at a remote site, as well as over the internet. The system architecture includes a Java user interface, CORBA middleware, an application server to run the classification and detection algorithms, and a database consisting of patient's medical history, the patient's medical images, and verbal and numerical information describing the medical images. This work was reported at the 2000 SPIE Meeting on Medical Imaging. A copy of this paper is provided here in Appendix 2.

The Java user interface has five components: a) patient data entry, b) radiologist worklist, c) image viewer, d) CAD screen, and e) reporting screen. Each of these components controls a distinct aspect of the system. The patient data entry component enables the entry of patient data and the digitizing of films. The radiologist worklist component provides a convenient means of assigning a distinct list of cases to each radiologist. The radiologist worklist screen also provides a convenient means of ensuring patient data security, in accordance with the privacy protocols of our Institutional Review Board (IRB).

The image viewer provides radiologists with several tools to enhance the visibility of abnormalities in the displayed mammograms. These tools include magnification of regions of interest, zoom in and zoom out, invert the image, change the contrast by adjusting the window and level settings, and move the image. Other tools include the selection of regions of interest (ROIs) for diagnosis and inclusion in the database. The image viewer also enables the radiologist to navigate among various images. For example the radiologist can view the left breast images (LCC and LMLO), and then command the system to display the right breast images (RCC and RMLO).

The CAD screen enables computer-aided diagnosis. On this screen the radiologist can view the eight ROIs in the database that are most similar to the ROI under study. Each of these eight ROIs is prominently marked as either malignant or benign. This screen also enables the radiologist to navigate through the entire database to search for images similar to the image under study.

The reporting screen enables a radiologist to select case descriptors from a comprehensive list of descriptors. The system then can print a report for the patient under study.

In response to a grant from the California Telehealth and Telemedicine Center (CTTC) to establish a telemammography system, we constructed CORBA middleware to enable remotely sited database-aided diagnoses. In this system, a radiologist at a remote site uses a centrally sited database as aid to diagnosis.

Our diagnostic system was demonstrated at *infoRAD* 2000, which was a section of the Annual Meeting of the Radiological Society of North America (RSNA) in November 2000. The RSNA

awarded our exhibit a Certificate of Merit for its “excellent content” and its “educational effectiveness.”

With the assistance of the grant from the CTTC, we developed a plan to test our database-aided diagnostic system remotely at the Humphrey Telehealth and Telemedicine Center. Since our diagnostic system is not approved for clinical use by the U.S. Food and Drug Administration (FDA), we developed a protocol for this test that would safeguard patients’ safety in the face of possible errors by the diagnostic system. A copy of this protocol is in Appendix 4.

Task 7. Retrospective test. (months 18-26)

- a. Using the data set obtained in Task 3a, carry out a test of the neurodatabase system with the five- radiologist reading panel in the computer-aided orientation described in the Proposal Body (months 18-19)
- b. Modify the neurodatabase system and revise the test set to accommodate the expanded database produced by Task 3h, following the procedures of Task 5. In the revised test set do not include any members of the test set of Task 7a. Using the revised test set and modified neurodatabase system, carry out a test with five radiologists in the computer-aided orientation described in the Proposal Body. (months 20-24)
- c. Using the modified test set and modified neurodatabase system, carry out a test with four radiologists in the radiologist-aided orientation described in the Proposal Body. (months 30-31)

POSTPONEMENT OF TASK 7:

A temporary shutdown of all IRB-approved research at Drew University in July 2000 imposed a delay in carrying out Task 7. While waiting for this approval we developed an enhanced architecture for our diagnostic system, which we described above in “Research Accomplishments for Task 6.” We plan to carry out Task 7 in Year 3.

RELEVANCE OF THE THIS WORK TO THE ORIGINAL HYPOTHESIS.

The following is our original hypothesis: *Compared to an unaided radiologist a neurodatabase diagnostic system assisting a radiologist in mammographic screening can significantly reduce both the incidence of negative biopsies as well as the incidence of missed cancers.*

The published paper (provided in Appendix 1) shows the validity of this hypothesis when the image data are restricted to regions of interest containing either microcalcifications or normal tissue.

KEY RESEARCH ACCOMPLISHMENTS

We expanded and refined our software for classifying microcalcifications and masses

- We acquired and organized a database of proven mammographic cases from 45 patients at the King/Drew Medical Center (KDMC) and 280 cases at the University of California at Los Angeles (UCLA).
- We refined and expanded the capabilities of our graphical user interface.
- We designed, built, and carried out preliminary tests of a framework for integrating the classifiers of microcalcifications and masses.
- We constructed a graphical user interface and a computer architecture that will work effectively at a remote site, as well as over the internet.
- We designed and constructed a platform-independent architecture for multisatellite remotely aided diagnosis of mammograms.

REPORTABLE OUTCOMES

Manuscripts, abstracts, articles, presentations:

J. Sklansky, Eric Y. Tao, M. Bazargan, C.J. Ornes, R.C. Murchison, S. Teklehaimanot, "Computer-Aided, Case-Based Diagnosis of Mammographic Regions of Interest Containing Microcalcifications," *Academic Radiology*, Vol. 7, No. 6, June 2000, pp. 395-405.

Jack Sklansky, EngScD, Chester J. Ornes, MS, "Database-Aided Diagnosis in Digital Mammography," *infoRAD* Exhibit, 2000 Annual Meeting of the Radiological Society of North America, November, 2000.

Chester Ornes, Daniel J. Valentino, Hong-Jun Yoon, Jack I. Eisenman, Jack Sklansky, "A Search Engine for Remote Database-aided Interpretation of Digitized Mammograms," *Proceedings of SPIE* 2000,

Chester Ornes, MS; Hong-Jun Yoon, MS; J. Sklansky, EngScD, exhibit of "Computer-Aided Interpretation of Mammograms," at I AM WOMAN conference on women's health, June 9, 2001, Irvine, California.

Award received:

Jack Sklansky and Chester Ornes received a Certificate of Merit for their *infoRAD* Exhibit on "Database-Aided Diagnosis in Digital Mammography" at the Annual Meeting of the Radiological Society of North America, November, 2000.

Funding based on work supported by this project:

"Database-Aided Telemammography," grant of \$115,000 from California Telehealth and Telemedicine Center, for the period April 1, 2000 to June 30, 2002. Project Director: Jack Sklansky, EngScD.

Employment or research opportunities applied for and/or received on experiences/training supported by this award:

Farnoosh Nooryanni, MD, received and accepted an offer of a residency in Radiology at the University of Southern California with the help of her experience as a Radiology Fellow on our project. This appointment will begin in July 2001.

Yvette Price, MD, received and accepted an appointment as a Radiology Fellow at the UCLA Iris Cantor Center for Breast Imaging, beginning in July 2001. Dr. Price was a Radiology Resident and participated in our project's research at the time that she applied for this Fellowship. She passed the Radiology Board Examination in 2001.

Ramin Poursani, MD, received and accepted an appointment as a Resident in Family Medicine at the University of Texas, San Antonio, beginning in July 2001. Dr. Poursani was a Radiology Fellow in our research project at the time that he applied for this Residency.

CONCLUSIONS

Our diagnostic system has advanced from a system restricted to a single region of interest, and with the lesions within each region of interest restricted to microcalcifications to a system in which more than one region of interest may be associated with each case, and in which the surrounding parenchymal tissue may be taken into account.

Our design of a platform-independent architecture for multisatellite remotely sited diagnosis of mammograms coupled with our enhanced ability to find similarities among multi-mammogram cases shows promise of contributing to the development and growth of multisatellite teleradiology.

Our advances in the development of JAVA-based image processing and image retrieval architectures on PC platforms enhances our ability to realize our diagnostic system with low-cost PC computers in conjunction with state-of-the-art high-resolution radiological monitors.

REFERENCES

1. J. Sklansky, Eric Y. Tao, M. Bazargan, C.J. Ornes, R.C. Murchison, S. Teklehaymanot, "Computer-Aided, Case-Based Diagnosis of Mammographic Regions of Interest Containing Microcalcifications," *Academic Radiology*, Vol. 7, No. 6, June 2000, pp. 395-405.
2. Jack Sklansky, EngScD, Chester J. Ornes, MS, "Database-Aided Diagnosis in Digital Mammography," *infoRAD Exhibit*, 2000 Annual Meeting of the Radiological Society of North America, November, 2000.

3. Chester Ornes, Daniel J. Valentino, Hong-Jun Yoon, Jack I. Eisenman, Jack Sklansky, "A Search Engine for Remote Database-aided Interpretation of Digitized Mammograms," *Proceedings of the 2001 SPIE Meeting on Medical Imaging Imaging, PACS and Integrated Medical Information Systems: Design and Evaluation*, Volume 4323, February 2001.

APPENDICES

Appendix 1. Reprint of article: J. Sklansky, Eric Y. Tao, M. Bazargan, C.J. Ornes, R.C. Murchison, S. Teklehaimanot, "Computer-Aided, Case-Based Diagnosis of Mammographic Regions of Interest Containing Microcalcifications," *Academic Radiology*, Vol. 7, No. 6, June 2000, pp. 395-405.

Appendix 2. Summary of paper: Chester Ornes, Daniel J. Valentino, Hong-Jun Yoon, Jack I. Eisenman, Jack Sklansky, "A Search Engine for Remote Database-aided Interpretation of Digitized Mammograms," *Proc. of the 2001 SPIE Meeting on Medical Imaging, PACS and Integrated Medical Information Systems: Design and Evaluation*, Volume 4323, February 2001.

Appendix 3. Form for mammographic assessment and findings; list of pathology codes.

Appendix 4. Research protocol for database-aided telemammography.

Appendix 5. Abstract of *infoRAD* 2000 exhibit.

Appendix 6. Curriculum Vitae of Jack Sklansky, EngScD.

APPENDIX 1.

Reprint of article: J. Sklansky, Eric Y. Tao, M. Bazargan, C.J. Ornes, R.C. Murchison, S. Teklehaymanot, "Computer-Aided, Case-Based Diagnosis of Mammographic Regions of Interest Containing Microcalcifications," *Academic Radiology*, Vol. 7, No. 6, June 2000, pp. 395-405.

Computer-aided, Case-based Diagnosis of Mammographic Regions of Interest Containing Microcalcifications¹

Jack Sklansky, EngScD, Eric Y. Tao, PhD, Mohsen Bazargan, PhD
Chester J. Ornes, MS, Robert C. Murchison, MD, Senait Teklehaymanot, MPH

Rationale and Objectives. The purpose of this study was to evaluate the effectiveness of a mapped-database diagnostic system in reducing the incidence of benign biopsies and misdiagnosed cancers among mammographic regions of interest (ROIs).

Materials and Methods. A novel neural network was devised (*a*) to respond to a query ROI by recommending to biopsy or not to biopsy and (*b*) to map each ROI in the database as a dot on a computer screen. The network was designed so that clusters in the array of dots help the radiologist to find proved ROIs visually similar to the query ROI. This mapped-database diagnostic system was restricted to ROIs with visible microcalcifications. The neural network was trained with a stored database of 80 biopsy-proved ROIs.

Results. Four radiologists acting independently on 100 ROIs recommended biopsies for 18, 15, 28, and 18 benign ROIs and misdiagnosed cancers in 11, 12, 7, and eight ROIs, respectively. Interaction with the mapped-database system reduced the numbers of benign biopsies to 11, eight, 18, and 10 cases and of misdiagnosed cancers to eight, seven, four, and three cases, respectively. Statistical analysis indicated that three radiologists achieved significant improvements at $P \leq .02$ and the fourth achieved a substantial improvement at $P \leq .07$.

Conclusion. By using a mapped database of proved mammographic ROIs containing microcalcifications, radiologists may statistically significantly reduce the numbers of benign biopsies and misdiagnosed cancers.

Key Words. Computer-aided diagnosis; digital mammography; microcalcifications.

A critical aspect of mammographic diagnosis is deciding whether to recommend biopsy. Approximately two benign lesions are sampled for biopsy for every malignant lesion detected (1). In a recent study of 2,400 women undergoing mammographic screening during a 10-year period (2), an additional \$33 was spent on evaluating false-positive re-

sults for every \$100 spent on screening. Among the women in that study, the cumulative risk of a false-positive result after 10 mammograms was 49.1%. Thus, it would be highly desirable to reduce the frequency of benign biopsies during mammographic screening without increasing the number of missed cancers.

The objective of this study was to evaluate the effectiveness of a recently devised "mapped-database diagnostic system" in reducing the frequency of benign biopsies and misdiagnosed cancers among mammographic regions of interest (ROIs). The principal difference between this system and earlier computer-aided diagnostic systems for mammography is the facilitation of diagnostic reasoning by a database of proved ROIs. In this study, the presented mammographic images and stored database are restricted to ROIs, and the ROIs themselves are restricted to those revealing apparent microcalcifications.

Interpretation of mammograms consists of two major components: *detection* and *diagnosis*. In detection, the

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radiologist typically examines four full-field views—two views of each breast. In these views, the radiologist may detect one or more ROIs revealing possible lesions. In diagnosis, the radiologist analyzes one or more ROIs to determine whether biopsy should be performed or whether the patient should be recalled for further examination. Thus, analysis of ROIs is an important part of clinical mammography, particularly in establishing a diagnosis. This study focused on the ability of the mapped-database diagnostic system to reduce the number of negative biopsy results and of misdiagnosed cancers associated with the analysis of ROIs.

By restricting the images used in this study to ROIs, thereby excluding the full-breast views, we reduced much of the cost and duration of the experiments, but at the expense of eliminating contextual evidence. A further reduction in cost—and in diagnostic accuracy—was obtained by replacing film mammograms with digital images displayed with a cathode ray tube monitor (3). By anticipating the widespread growth of digital mammography while recognizing these reductions in diagnostic accuracy, this relatively inexpensive study examined the effect of the mapped-database system on diagnostic accuracy during digital mammography.

In the mapped-database system, an artificial neural network responds to a mammographic ROI by recommending, or not recommending, biopsy. In addition, the neural network maps a database of ROIs from proved mammograms onto a two-dimensional display as an aid to establishing a diagnosis. The network does this by mapping each ROI into a dot on a screen and arranging these dots so that they cluster into radiographically similar subclasses. We refer to this representation as a *mapped database*. In addition to producing the mapped database, the neural network partitions the screen into two decision regions: one for a biopsy being recommended, and the other for a biopsy not being recommended. We call the resulting display a *relational map* (4). By annexing this neural network to a means of quickly retrieving and viewing ROIs that are mapped close to the query, the radiologist is given a simple way of conversing with the database to enhance the reliability of the diagnostic decision. Thus, this system amplifies the radiologist's powers of "case-based reasoning" (5) and acts somewhat like a second reader with consensus (6).

This concept led to construction of a mammographic diagnostic system built on the basis of several earlier developments: (a) algorithms for detecting and analyzing clusters of microcalcifications (7–10), (b) large databases of digitized mammograms (11–15), (c) genetic algorithms for high-speed parallel search (16), and (d) "visual neural classifiers" (ie, specialized neural networks) that map multidimensional features and multidimensional decision surfaces

onto two-dimensional displays (4). We refer to this as a *mapped-database diagnostic system*. The test results reported herein suggest that for mammograms with detectable microcalcifications, this system can provide a new level of reliability for mammographic diagnosis.

The most pertinent earlier work regarding database-aided mammographic diagnosis is that by Swett and his colleagues at Yale University (17). Their mammographic database system, MAMMO/ICON, required a verbal medical history and verbal mammographic descriptors to supplement each mammogram. This system could provide diagnostic advice that depended on semantic similarities of the verbal descriptors and medical histories (18). A shortcoming of this technology, however, was its dependence on verbal descriptors to match information that was essentially pictorial and nonverbal. Among radiologists, there may be considerable variability in the specific words used to describe the pertinent properties of any given mammogram. This variability may impair the reliability of retrieving similar mammograms filed according to verbal descriptors. Another shortcoming was the manual construction of the verbal descriptors for the mammograms, in contrast to the possibility of automatic extraction and counting of key words in text.

Among other published articles on computer-aided diagnosis of mammograms, those by Getty et al (19), Jiang et al (9), and Chan et al (20) are particularly relevant to the present work. Getty et al (19) demonstrated that a checklist of descriptors (ie, "features") combined with a digital classifier could be an effective aid in establishing the diagnosis during mammography. These features, as in our experiment, were for the most part descriptors of a "focused abnormality" (ie, the equivalent of ROI as used here). The protocol for aiding the radiologist included a computer-alone reading, which was followed with a second reading by the radiologist (analogous to a double reading with consensus). A second contribution by Getty et al was the demonstration that a carefully selected set of features, when coupled with a session to train radiologists to estimate these features, could enable computer-aided generalists to read film mammograms almost as well as highly skilled specialists. Jiang et al (9) demonstrated the potential of automatically extracting features from microcalcifications, coupled with an artificial neural network, for computer-aided diagnosis. The methods in both of these studies (9,19), however, still required substantial human involvement in the computer-aided procedure. In the method of Getty et al (19), each radiologist estimated the numeric level of intensity or level of confidence for the existence of each feature; in the method of Jiang et al (9), the location of each microcalcification was determined manually. This

amount of human involvement likely makes these techniques impractical for clinical use.

Chan et al (20) restricted human involvement to identifying in each view an ROI enclosing a mass. This level of human involvement is likely to be practical during clinical applications, because finding ROIs is part of the usual procedure for interpreting mammograms. As in the method of Getty et al (19), the radiologist-reader in the method of Chan et al (20) was asked to make a final estimate regarding the likelihood of malignancy in a presented mammogram after first performing an unaided estimation and then receiving the computer's estimate. In that study, the performance of the computer alone was comparable to that of the best performing unaided radiologist-reader and to the performance of six aided radiologist-readers as a group.

MATERIALS AND METHODS

A retrospective study of the mapped-database system was performed during June 1998. The ROIs included in this study were restricted to those exhibiting microcalcifications. For this study, we acquired a database of 200 ROIs from 138 proved cases. Biopsy results were included with each ROI. Four radiologists from the clinical faculty of the Department of Radiology at King/Drew Medical Center (KDMC) read the digitized images in this study. None of these radiologists was familiar with the cases, and all of them were certified for mammography by the U.S. Food and Drug Administration. Their postresidency experience in reading mammograms was 29 years, 10 years, 5 years, and 6 months; these readers are referred to as R₁, R₂, R₃, and R₄, respectively.

The ROIs in the database were excised from digitizations of film mammograms provided by KDMC and by the University of California at Los Angeles (UCLA) Iris Cantor Center for Breast Imaging. In all cases associated with these mammograms, either biopsy or follow-up with subsequent mammography was performed. From these mammograms, all 138 cases that revealed microcalcifications were selected for this study. Fifty-two cases were from KDMC, and 86 were from UCLA. The selected mammograms were digitized at KDMC on a scanner-digitizer (Lumiscan 85; Lumisys, Sunnyvale, Calif) at a pixel width of 50 µm and a pixel depth of 12 µm.

For each film mammogram, the location of an abnormality containing a cluster of microcalcifications was provided in the medical record that accompanied the image. From this information, we constructed a 512 × 512-pixel ROI enclosing each designated cluster of microcalcifications. This construction yielded 160 ROIs. No two ROIs in this set were views of the same lesion. To each ROI we ap-

plied an automatic microcalcification detector and segmenter that was developed during an earlier study (7). An additional 40 normal ROIs were also added to this database, thereby making a total of 200 ROIs in this study. These normal ROIs were included to ensure that readers would have the impression that not all ROIs in the set used to test the system (described later) were abnormal. The normal ROIs were obtained from cases involving patients who did not undergo biopsy and were not recalled during a period of at least 18 months. Within each of these cases, the normal ROI was selected arbitrarily.

Of the abnormal ROIs (ie, those containing microcalcifications), 64 were proved at biopsy to be benign, 49 were proved at biopsy to be malignant, and 47 were proved at follow-up to be benign (ie, both the ROI and the follow-up findings did not produce a recommendation for biopsy). At least 18 months elapsed between two successive examinations, and none of the radiologists on our reading panel had seen these ROIs before this study. One radiologist (R₁) partitioned the 200 ROIs into groups such that ROIs in the same group were visually similar. We refer to these groups as *perceptual groups*. No restriction was placed on the number of perceptual groups, although the radiologist (R₁) was informed that eight groups were formed by another radiologist during another set of ROIs in an earlier experiment (21). The radiologist (R₁) partitioned the 200 ROIs into the following 12 groups: (a) amorphous with mass, (b) lobular and ductal, (c) amorphous, (d) pleomorphic and scattered, (e) lobular, (f) granular, (g) casting, (h) punctate scattered, (i) linear ductal, (j) vesicular, (k) oil cyst, and (l) no visible abnormality.

Computer-aided reading of the test set by the reading panel was performed more than a month after partitioning of the ROIs into perceptual groups. The intent of this 1-month delay was to suppress the memory of the 200 ROIs in the radiologist who partitioned them into the perceptual groups.

The database was then divided into two sets, D and T, each of which consisted of 100 ROIs. D was used for the design of the diagnostic system, and T was used for testing of the system. The 160 abnormal ROIs were randomly partitioned several times into two equal parts, D_A and T_A, until a (D_A, T_A) pair was found such that D_A and T_A each contained at least two ROIs from each perceptual group. (Ensuring representation of at least two ROIs from each perceptual group, however, may have biased the diagnostic system somewhat in favor of the neural network. On the other hand, not achieving this representation would have biased the study against the neural network.) D_A consisted of 54 benign and 26 malignant ROIs. T_A consisted of 57 benign and 23 malignant ROIs. Because no two ROIs were images of the same lesion, all lesions in T

Table 1
Features Extracted from Microcalcifications and Regions of Interest

Feature	Symbol	Formula	Clinical Importance
Area	A	Number of pixels in the calcification labeled ≥ 0	Large calcification may suggest a benign abnormality.
Perimeter	P	Number of pixels in central boundary (label = 0)	Large calcification may suggest a benign abnormality.
Irregularity	I	A/P^2	Irregular boundary may suggest a malignant abnormality.
Mean intensity	MI	Average brightness of pixels labeled ≥ 0	Bright calcification may suggest a benign abnormality.
Standard deviation of intensity	SI	Standard deviation of pixels labeled ≥ 0	Large SI may suggest an irregular density and malignancy.
Mean of exterior intensity	ME	Average brightness of pixels within 5 pixels from the calcification	Large ME may suggest a dense and malignant tissue.
Standard-deviation of exterior intensity	SE	Standard deviation of pixels within 5 pixels from the calcification	Large SE may suggest a malignant tissue.
Contrast	C	$ MI - SI - MI$	Large contrast may suggest a benign abnormality.
Sharpness of boundary	SH	Average change in brightness between pixels labeled 0 or 1 and those labeled -1 or -2	Large SH may suggest a benign abnormality.
Inner shell contrast	B_1	Average change in brightness between pixels labeled 2 and those labeled 1	Large B_1 may suggest a benign abnormality.
Center shell contrast	B_0	Average change in brightness between pixels labeled 1 and those labeled 0	Large B_0 may suggest a benign abnormality.
Outer shell contrast	B_{-1}	Average change in brightness between pixels labeled 0 and those labeled -1	Large B_{-1} may suggest a benign abnormality.
Exterior shell contrast	B_{-2}	Average change in brightness between pixels labeled -1 and those labeled -2	Large B_{-2} may suggest a benign abnormality.
Concavity index	CI	Area of region between the calcification and its convex hull	Large CI may suggest a malignancy.
Shape signature	SG	$\left[\int r(\theta) - R d\theta \right] / R$, where r is radial distance of boundary from centroid, R is the mean of r , and θ is orientation of r	A large SG may suggest benign tissue.
Aspect ratio	R	Ratio of maximum central diameter to minimum central diameter	Large R may suggest a malignancy.
Count	N	Number of calcifications	Large count may suggest malignancy.
Structural index	S	$1 - d \sqrt{(N/AC)}$, where d is the average distance of the closest calcification and AC is area spanned by cluster	Large S indicates nonuniform distribution of microcalcifications and, hence, may suggest malignancy.

were distinct from all lesions in D . The 40 normal ROIs were partitioned several times into two equal parts, D_N and T_N , until a (D_N , T_N) pair was found such that D_N and T_N had similar distributions in the mapped feature space. The final design set D was the union of D_A and D_N . The final test set T was the union

of T_A and T_N . These procedures were performed to ensure the design set was representative of the types of abnormalities occurring in the test set. As mentioned, the normal ROIs were included to ensure the readers would have the impression that not all ROIs in T were abnormal. Because diagnostic (rather

-3	-2	-2	-2	-1	-1	-1	-2	-2	-3
-2	-1	1	-1	0	0	0	-1	-1	-2
-1	0	0	0	1	1	1	0	0	-1
-1	0	1	1	2	2	2	1	0	-1
-1	0	1	2	2	2	2	1	0	-1
-1	0	1	2	1	1	1	0	0	-1
-1	0	1	1	0	0	0	-1	-1	-2
-1	-1	0	0	-1	-1	-1	-2	-2	-3
-2	-2	-1	-1	-2	-2	-2	-3	-3	-4

Figure 1. Numeric labeling for the pixels of a digital model representing a typical microcalcification. The label of each pixel is the number of pixel displacements of that pixel from the medial axis of the boundary of the microcalcification. Thus, 0 denotes a pixel on the medial axis of the boundary, 1 a pixel just inside the boundary, -1 a pixel just outside the boundary, and -2 a pixel just outside the -1 region.

than detection) efficacy was paramount in this study, the mapped-database system in this study was designed to analyze only the abnormal ROIs. Consequently, readings of the normal ROIs were not included in our calculations of specificity, sensitivity, and other measures of performance.

From each abnormal ROI, 18 candidate features were extracted. Each candidate feature was designed to reflect one or more properties of calcifications (or groups of calcifications) that are meaningful to the radiologist. These features were based on the American College of Radiology's Breast Imaging Recording and Data System (BI-RADS) descriptors for interpreting mammograms, the book by Lanyi (22), and discussions with the radiologists on our panel. Unfortunately, most BI-RADS descriptors are too subjective for encoding into computer-executable formulas. Consequently, the features we extracted were inspired by, but not necessarily a direct implementation of, the BI-RADS descriptors. A formulation and brief clinical justification for each of these features are given in Table 1. In the first two columns of this table, a name and a mathematical symbol denote each feature. A formula for each feature is given in the third column. The fourth column contains a brief description of the clinical importance of the feature. Some of the formulas refer to numerical pixel

labels -2, -1, 0, and 1. The label on each pixel P is the number of pixel displacements of P from the boundary of a calcification. The label 0 denotes a pixel on the boundary, 1 denotes a pixel just inside the boundary, -1 denotes a pixel just outside the boundary, and -2 denotes a pixel just outside the -1 region. These labels are illustrated in Figure 1, which shows a digital model of a typical microcalcification.

Starting from this set of candidate features, a genetic algorithm searched for those subsets of features that were most effective in discriminating malignant from benign cases in the database. This algorithm was designed in accordance with the genetic feature selector described by Siedlecki and Sklansky (23). In this algorithm, each candidate subset is represented by a binary string (ie, a sequence of 0s and 1s). The value (0 or 1) of the *n*th element of the string indicates whether the *n*th feature belongs to the candidate subset. We refer to this string as a *chromosome*. A population of 100 chromosomes was transformed by an evolutionary process consisting of mutation, mating, and reproduction to form a sequence of new populations or "generations" under the guidance of a penalty function that accounted for the *k*-nearest-neighbor discriminability of the feature vectors in each feature subset and for the number of features in the subset. The sizes of the new populations were kept constant at 100. This evolutionary process also optimized the value of *k*. To ensure an acceptably low rate of misdiagnosed cancers, the penalty function gave seven times as much weight to misdiagnosing a cancer as to recommending a biopsy that was benign. (The weight was chosen empirically so that the nearest-neighbor classifier would produce only one or two missed cancers on the data set.) This algorithm selected the following four features: (a) mean area, (b) mean aspect ratio, (c) mean irregularity (ie, noncircularity), and (d) number of microcalcifications. Another algorithm extracted these four features from each ROI, thus forming a four-dimensional *feature vector* as a descriptor of that ROI.

A five-layer neural network was constructed in accordance with the architecture and the design principles described by Ornes and Sklansky (24). Each node in this architecture represented an artificial neuron that consisted of a weighted summation followed by a sigmoidal activation function. The first layer consisted of four input neurons, one for each selected feature. The second and third layers consisted of three and two neurons, respectively, to reduce the dimensionality of feature space. The two-neuron layer produced x and y coordinates (one from each of the two neurons) to represent each ROI as a dot on a relational map. For each ROI in the design set, this dot was labeled to indicate whether the biopsy was benign or malignant. The two

neurons in the fifth layer classified each feature vector as either "biopsy recommended" or "biopsy not recommended." (The neuron producing the larger of the two outputs determined the class of the feature vector.) By entering every permissible pair of map coordinates at the input to the fourth layer, the fifth layer thus produced a relational map in which all pixels were labeled as either biopsy recommended or biopsy not recommended.

Using the four features selected by the genetic algorithm, the neural network was trained by backpropagation (ie, a form of gradient descent in the space formed by the weights at the inputs to the neurons) on the design set D_A , thereby producing the trained neural network $NN(D_A)$ (4). In accordance with our design philosophy for this study, the neural network was trained only on abnormal ROIs. The biopsy outcomes (ie, benign and malignant) in the database were the desired output classes in the trained neural network, which produced a two-dimensional map of D_A and a near-optimal partition of this map into two decision regions. These decision regions were associated with the decisions of biopsy recommended and biopsy not recommended. The training was stopped when the mean square error converged to a nearly constant value. This design strategy, and the relatively low error rate of the neural network on the test set T , encouraged us to believe that the network was then adequately trained.

The boundary separating the decision regions is referred to as a *decision curve*. The decision curve is substantially smoother than the variability of the data, which is the result of the averaging produced by the backpropagation training and the small number of neurons compared with the number of feature vectors in the training set. The neural network tends to produce decision regions that are responsive to statistical models of the training data rather than to the training data itself. Specifically, the training algorithm minimized a weighted sum-of-squared-error function, which yielded outputs that were estimates of Bayesian posterior probabilities that the input vector belonged to the corresponding class (ie, biopsy recommended or biopsy not recommended). Thus, the decision curve produced by the neural network tends to "generalize" the training data and, thereby, to make good decisions on future data not included in the training set (25).

The trained neural network displayed the query and the ROIs in D_A as dots, with each dot being located by the x and y coordinates produced by the two neurons (one coordinate from each neuron) at the two-neuron layer of the network. We refer to the space spanned by x and y as the *mapped feature space* and to the map of D_A as a *mapped database*. The map of D_A and its decision regions are depicted in Figure 2. We call this a *relational map*. Here, the black region repre-

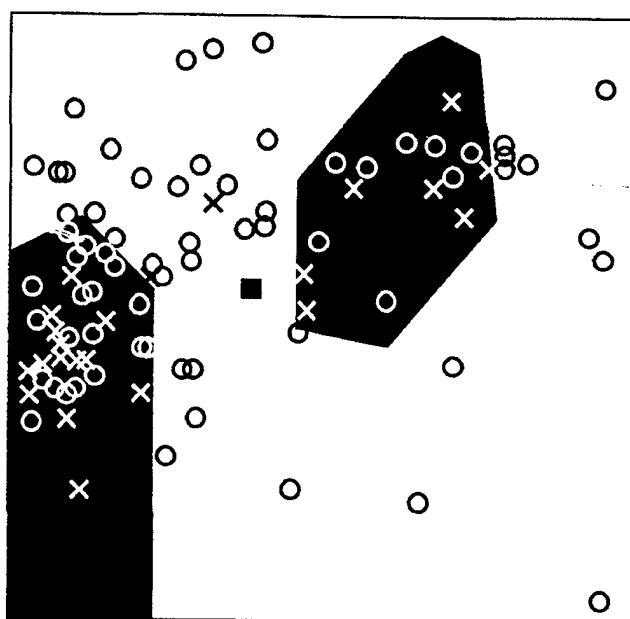


Figure 2. Relational map of design set D and the query ROI. Each malignant case is labeled X, and each benign case is labeled O. The query ROI is labeled ■.

sents biopsy recommended, and the white region represents biopsy not recommended. The decision curve is the boundary between the black and the white regions. The symbols O and X denote benign and malignant feature vectors, respectively. The symbol ■ denotes a query.

A weakness of the mapped-database system is that it does not reveal the quantitative relationships between the mapped feature space and the unmapped features. This weakness is compensated for, however, by the ability of the relational map to cluster visually and diagnostically similar ROIs and by the map's representation of a multidimensional decision surface as a decision curve (or as several disjoint decision curves) in the mapped feature space. The clustering helps the radiologist to find ROIs that are visually similar to the query, and the decision curve helps the radiologist to determine the confidence of the neural network in its recommendations either for or against performing biopsy. Further insight into the relationships between the mapped feature space and the original features can be obtained by making available the numerical values of the original features of each mapped ROI to the radiologist-user.

The user interface presented on the computer monitor is illustrated in Figure 3. This interface guides the radiologist-user through the steps of diagnosis. Identification numbers in this figure (eg, 011318) were constructed so that patients could not be identified from the information in the figure. The mammographic image in the upper left is an enlargement of the ROI

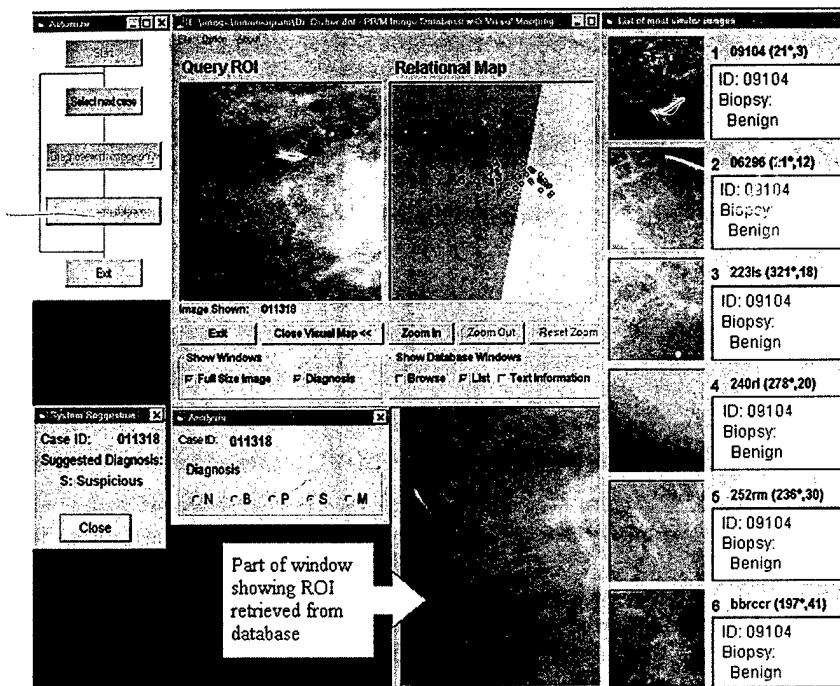


Figure 3. User interface for mammographic diagnosis.

of a query mammogram. Digital magnification and negative-to-positive inversion were provided as options on the user interface. In response to a prompt from the interface, the radiologist first determines an "unaided" diagnosis of this ROI and reports it in the BI-RADS code (26) by clicking N, B, P, S, or M, which denote normal, benign, probably benign, suspicious (possibly malignant), and almost definitely malignant, respectively. In this study, we assumed that N, B, and P corresponded to biopsy not recommended and that S and M corresponded to biopsy recommended. This assumption conformed to the clinical practice at KDMC. We instructed each reader to produce the unaided diagnosis as if it were the final diagnosis for the examination. No time limit was imposed on this diagnosis.

In this study, the diagnostic process began by establishing an unaided diagnosis, which was followed immediately by establishing an aided diagnosis (analogous to double reading). We assumed that the operating point (ie, the subjective decision threshold for a BI-RADS symbol) of the unaided radiologist might be affected by that radiologist's anticipation of an aided diagnosis, but that the receiver operating characteristic (ROC) of the unaided diagnosis was unaffected by that anticipation.

Immediately after the unaided diagnosis was established, the relational map was presented to the radiologist. This map contained the mapped database, mapped query, and distinctively colored decision regions. Thumbnail images of six

ROIs near the query in the mapped feature space were presented at the right of the monitor screen. From these images, the radiologist retrieved for review those with a visual appearance that seemed to be most similar to that of the query. This review was facilitated by an enlarged view of the retrieved ROI and the accompanying biopsy reports. On the basis of this interaction, the radiologist selected a BI-RADS score for the ROI. Again, the reader was not restricted by a time limit for establishing this diagnosis, and both magnification and inversion were provided as options on the user interface.

To evaluate the diagnostic improvement provided by the mapped-database diagnostic system, we computed the ROC of each unaided radiologist, of each computer-aided radiologist, and of the computer alone. Each ROC accounted for the BI-RADS responses of the radiologists and for the outcomes of the biopsies. The diagnostic performance of each radiologist was measured by the area A_z under the ROC curve, which is an estimate of the probability for a correct decision in a forced choice between two ROIs, one of which is malignant and the other of which is benign (27). Thus, A_z must lie between a minimum of 0.5 (corresponding to an unbiased random guess) and a maximum of 1 (perfect performance).

We also computed the average performance of the four radiologists when unaided by the mapped-database system and when aided by the mapped-database system. LABMRMC (C.E. Metz, LABMRMC 1.0B, beta version 3, University of

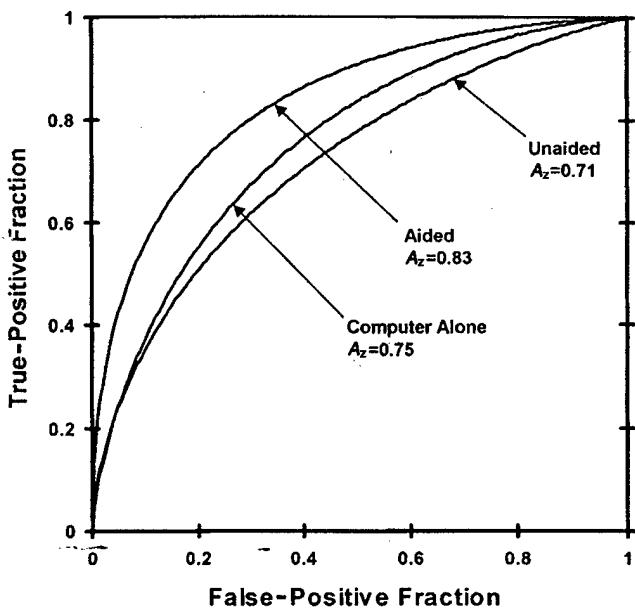


Figure 4. ROC curves for radiologist R_1 and for the computer alone.

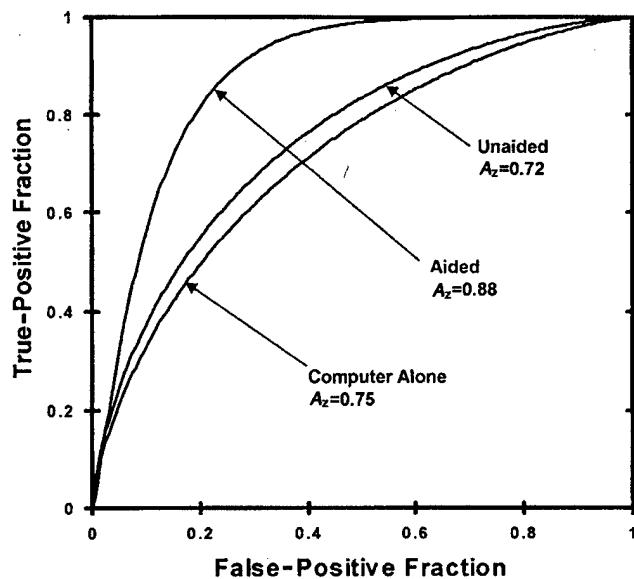


Figure 5. ROC curves for radiologist R_2 and for the computer alone.

Chicago, Chicago, Ill) (28) was employed to calculate the maximum likelihood estimates for the parameters of binormal models and the statistical significance of the change in areas under the ROC curves for the unaided and the aided reading modalities. The ROC curves representing the average performance of the unaided radiologists were computed by averaging their estimated slopes and intercepts in normal deviate space. This same process was also performed for the aided radiologists.

The mapped-database diagnostic system was designed and implemented at the University of California, Irvine, on an IBM-PC-compatible computer with a 66-MHz Intel 486 processor, 32 MB of random access memory, and a 17-inch CTX monitor with $1,280 \times 1,024$ pixels running on a Microsoft (Redmond, Wash) Windows 95 operating system. The software development environment was Microsoft Visual C++ 4.0 for image-processing functions and Microsoft Visual Basic 5.0 for the user interface. Testing of this system was performed at KDMC on another IBM-PC-compatible computer with a 233-MHz Pentium II processor, 64 MB of random access memory, and a 17-inch monitor (Vivitron; Gateway 2000, Sioux City, SD) with $1,280 \times 1,024$ pixels running on a Microsoft Windows 95 operating system.

RESULTS

The ROC curves, labeled by their A_z values, are shown in Figures 4–8. The statistical significance of the changes

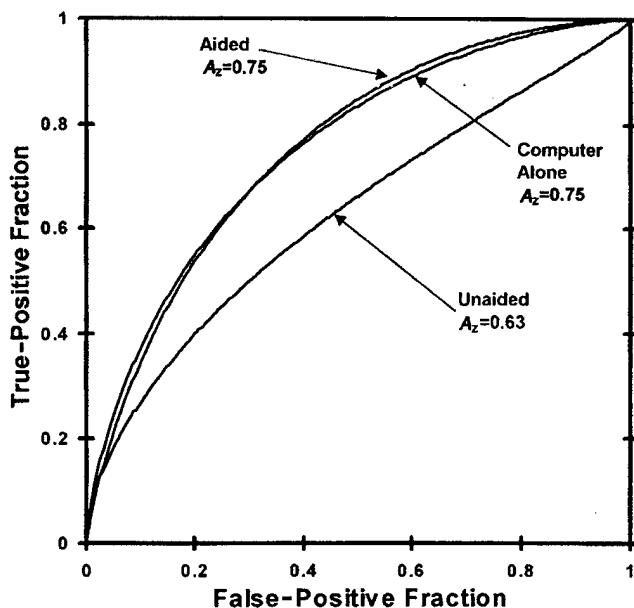


Figure 6. ROC curves for radiologist R_3 and for the computer alone.

in these A_z values is reported in Table 2. The columns of A_z values for the unaided radiologist, the aided radiologist, and the computer alone are labeled A, B, and C, respectively. The column labeled A-B denotes the values of P associated with the increase in A_z obtained by replacing an unaided radiologist with the corresponding aided radiologist. The values of P listed in Table 2 are two-tailed and

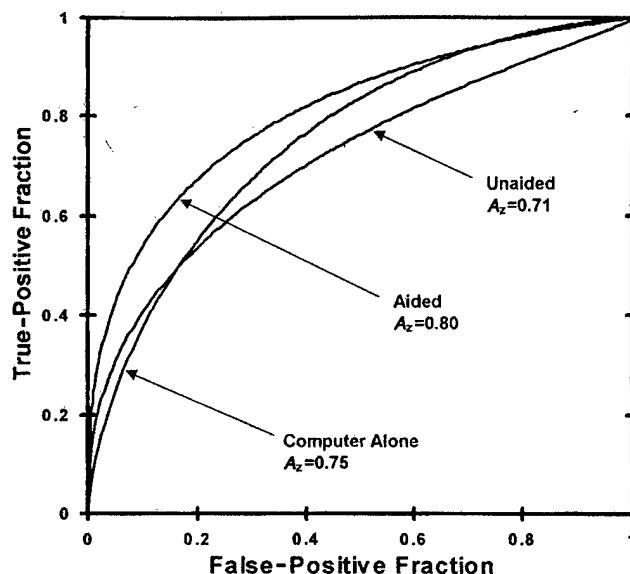


Figure 7. ROC curves for radiologist R_4 and for the computer alone.

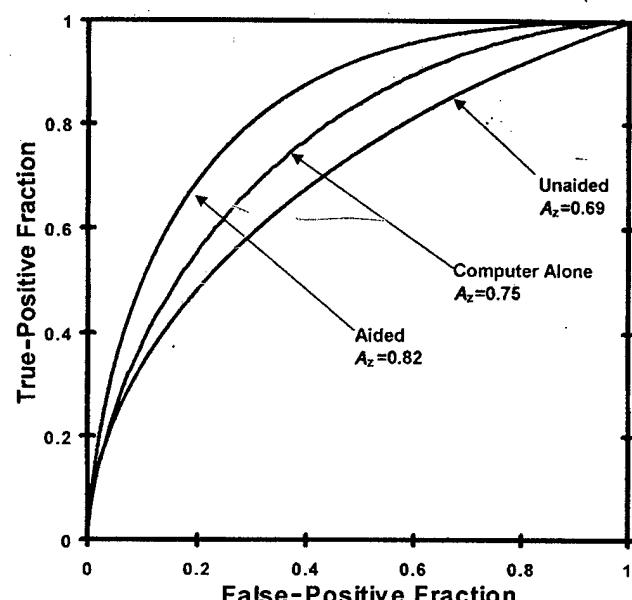


Figure 8. ROC curves for the average performance of the four radiologists.

Table 2
Comparison of ROC Curves for the Unaided Radiologist, the Aided Radiologist, and the Computer Alone

Reader	A_z			P
	A, Unaided	B, Aided	C, Computer Alone	
R_1	0.7150	0.8354	0.7533	0.0157
R_2	0.7179	0.8814	0.7533	0.0013
R_3	0.6277	0.7538	0.7533	0.0015
R_4	0.7157	0.8077	0.7533	0.0636

were calculated under the assumption that the distribution of each estimated change in A_z , divided by the estimated standard error of that change, arose from a normal distribution. These values of P were computed by using the ROCKIT software (C. E. Metz, ROCKFIT 0.9B, beta version, University of Chicago, Chicago, Ill, 1998).

The information in Figures 4–7 indicates that (a) every aided radiologist outperformed the same unaided radiologist, (b) no unaided radiologist outperformed the computer alone, and (c) three aided radiologists outperformed the computer alone and the fourth aided radiologist (R_3) performed approximately equal to the computer alone. The information in Table 2 indicates that the A_z values of the unaided radiologists ranged from 0.6277 to 0.7179, and that those of the aided radiologists ranged from 0.7538 to 0.8814. The size of the changes in A_z among the radiologists ranged from

0.0920 to 0.1635. Table 2 also indicates that the A-B changes in A_z (ie, unaided-to-aided changes in A_z) were statistically significant at $P < .002$ for radiologists R_2 and R_3 , at $P < .02$ for radiologist R_1 , and at $P < .07$ for radiologist R_4 . After application of the Bonferroni correction for multiple comparisons, these three P bounds became .008, .08, and .28, respectively (29). Other changes in A_z —namely, A-C (ie, unaided-to-computer alone changes) and B-C (ie, aided-to-computer alone changes)—were not statistically significant.

Figure 8 shows the average performance of the four radiologists when unaided by the mapped-database system and when aided by the mapped-database system. Results of the LABMRMC analysis indicate that performance of the aided radiologists, as a group, was statistically superior to that of the unaided radiologists as a group ($P < .05$).

At KDMC, the diagnostic scores S and M are conventionally interpreted as being biopsy recommended, and N, B, and P are interpreted as being biopsy not recommended. In accordance with this convention, we calculated the numbers of negative biopsies and misdiagnosed cancers, as well as the sensitivities and specificities of each radiologist, both aided and unaided by the mapped-database system. These results are shown in Tables 3–5. Tables 3 and 4 show the numbers of recommended benign biopsies and misdiagnosed cancers. Table 5 shows the sensitivities and specificities. The mapped-database diagnostic system helped every radiologist reduce the number of benign biopsies by 40% or more while simultaneously reducing the number of misdiagnosed cancers. All

Table 3
Numbers of Recommended Benign Biopsies for the Unaided Radiologist and the Aided Radiologist

Reader	Unaided Radiologist	Aided Radiologist
R ₁	18	11
R ₂	15	8
R ₃	28	18
R ₄	18	10
NN	24	...

Note.—Number of ROIs from benign cases: 57. NN = neural network.

the radiologists also increased both their sensitivities and specificities through their interaction with the mapped-database system. The statistical significances of these increases ranged from $P < .01$ to $\bar{P} \leq .12$ on the basis of a comparison of proportions (30).

As mentioned, the sensitivities, specificities, and ROCs were calculated on the basis of the 160 abnormal ROIs and the responses of the panel of radiologists to them. The responses of the panel of radiologists to the 20 normal ROIs (the remaining 20 normal ROIs were in the set D_N) were excluded from these calculations, because in this study, the mapped-database diagnostic system was designed only to interpret abnormal ROIs.

DISCUSSION

Figures 4–8 and Tables 2–5 indicate that the diagnostic performances of the aided radiologists were statistically significantly improved compared with those of the unaided radiologists. Table 2 shows that the sizes of these improvements in A_z for the current study are comparable to those in A_z found during a recent study concerning computer-aided characterization of mammographic masses (20).

We are also encouraged by the improved performance of the aided radiologists over that of the computer alone, as indicated in Figures 4, 5, 7, and 8 and in Table 2, although the number of cases was insufficient to prove statistical significance of these improvements. Table 5 shows that the mapped-database diagnostic system enabled substantial increases in specificities and sensitivities for all the radiologists in our panel. We conclude that for ROIs containing microcalcifications, the mapped-database diagnostic system shows promise in helping most radiologists to raise their diagnostic performances substantially over their unaided performances while providing relevant images from a proved database to support the radiologists' aided diagnoses. In particular, these radiolo-

Table 4
Numbers of Misdiagnosed Cancers for the Unaided Radiologist and the Aided Radiologist

Reader	Unaided Radiologist	Aided Radiologist
R ₁	11	8
R ₂	12	7
R ₃	7	4
R ₄	8	3
NN	4	...

Note.—Number of ROIs from malignant cases: 23. NN = neural network.

gists may achieve substantial reductions in the number of benign biopsies and misdiagnosed cancers.

The levels of postresidency mammographic experience among the radiologists in this study ranged from 29 years to 6 months (R₁ > R₂ > R₃ > R₄). Figures 4–7 suggest that all radiologists are likely to benefit substantially from access to the mapped-database diagnostic system regardless of their experience. This is important, because radiologists vary widely in their diagnostic skills—even among those who rate themselves as “experts” (31). Whether the size of the benefit correlates with the amount of experience, however, is not clear from Figures 4–7. (It is interesting that the performance of the aided R₂ exceeded that of the aided R₁, even though the experience of R₁ was greater.)

The results of this study suggest that a properly designed interface between a human reader and a proved database of mammographic images may enable less experienced readers to exceed the performances of unaided, highly skilled readers—without the need for time-consuming training on feature extraction as exemplified by Getty et al (19). Furthermore, our diagnostic system represents an improvement over earlier systems (17,19) by automating the selection of visual features.

This study was limited, however, by the quality of the monitors used for viewing the images, the size and comprehensiveness of the mammographic database, the lack of full-field and earlier views, the restriction of the lesions to microcalcifications, and a possible “reading-order effect” associated with the close succession of unaided and aided diagnoses (32). Our next investigation of the mapped-database diagnostic system will include several enhancements to overcome these limitations. The images will be viewed on state-of-the-art, high-resolution radiographic monitors, and the number of cases will be increased. The tested images will also include full-field craniocaudal and mediolateral oblique or lateral views of each breast, and the lesions

Table 5
Statistical Significance of Changes in Performance

Reader	Unaided Radiologist (%)		Aided Radiologist (%)		Change in Sensitivity		Change in Specificity	
	Sensitivity	Specificity	Sensitivity	Specificity	Change (%)	P	Change (%)	P
R ₁	47.8	73.7	69.6	86.0	+21.8	<.01	+12.3	.12
R ₂	65.2	68.4	87.0	82.5	+21.8	<.01	+14.1	<.05
R ₃	52.2	68.4	65.2	80.7	+13.0	.09	+12.3	.07
R ₄	69.6	50.9	82.6	68.4	+13.0	<.05	+17.5	<.05

will include both masses and microcalcifications. In addition, the aided and unaided diagnoses will be separated by at least 1 month.

ACKNOWLEDGMENTS

The panel of radiologists consisted of Anthony C. Dishner, MD, Robert C. Murchison, MD, Janis F. Owens, MD, and Carolyn R. Towler, MD. Jack I. Eisenman, MD, at KDMC assisted in searching the literature and reviewing the manuscript. We thank Lawrence W. Bassett, MD, at the University of California, Los Angeles, for providing access to his file of film mammograms. We are grateful to Charles E. Metz, PhD, and Benjamin A. Herman, BA, at the University of Chicago for providing the software for ROC analysis and advice in the use of this software. We also thank Farrooosh Nooryani, MD, and Jorge Navarrete, MD, for several helpful discussions, Phyllis Bryant for her careful preparation of Figures 5–9, and Helen Lee, BA, for formatting the manuscript.

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APPENDIX 2

Summary of paper: Chester Ornes, Daniel J. Valentino, Hong-Jun Yoon, Jack I. Eisenman, Jack Sklansky, "A Search Engine for Remote Database-aided Interpretation of Digitized Mammograms," *Proc. of the 2001 SPIE Meeting on Medical Imaging, PACS and Integrated Medical Information Systems: Design and Evaluation*, Volume 4323, February 2001.

SUMMARY
SPIE: MEDICAL IMAGING 2001

- 1. SUBMIT TO:** mi05 Siegel, Huang
- 2. TITLE OF CONFERENCE:** PACS and Integrated Medical Information Systems: Design and Evaluation
- 3. PAPER TITLE:** A search engine for remote database-aided interpretation of digitized mammograms.
- 4. AUTHOR LISTING:**

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5. PRESENTATION PREFERENCE: Oral Presentation

6. FIVE-PARAGRAPH SUMMARY:

We describe a web-based image-by-content search engine for teleradiology. This search engine enables radiologists to access a large database of diagnostically proven mammographic regions of interest (ROIs) as an aid in the interpretation of mammograms.

The image search engine is based on a neural network that maps the image database into a "relational map." In the relational map each region of interest (ROI) in the database is color-coded as a point denoting "benign" or "malignant." Points that are close together represent similar images, where "similar" is defined by several perceptual measures. Points that are far apart represent dissimilar images. Clusters of points may represent a group of ROIs associated with the same breast disease. An example of a relational map is shown in the figure.

The radiologist selects a query ROI from a full mammogram, and presents the query ROI to the search engine. The radiologist may browse the database by identifying points in the relational map that are near to and belong to the same cluster as the query. Alternatively the radiologist may command the search engine to retrieve several (usually five or six) ROIs that are close to the query in the relational map. The search engine also presents the biopsy results and other patient information for the retrieved ROIs. This type of search facility helps the radiologist to incorporate subtle image relationships into the diagnostic process.

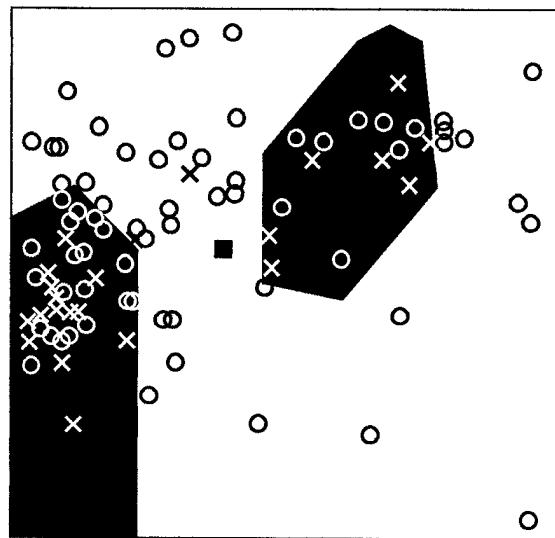
The search engine is configured in a 3-layer distributed architecture. The first layer is the user interface. This interface is a JAVA applet that allows a radiologist to acquire a digital mammogram, to enhance the mammogram, to select an ROI, and to query the database. The second layer contains a web-server to provide the HTML web pages, image processing algorithms to extract a library of image features, and the neural network to create the relational map and provide the image search functions. The third layer is the remotely sited database of ROIs and associated patient information. The patient information includes biopsy results, if available. The individual layers communicate with each other using the Common Object Request Broker Architecture (CORBA). CORBA is middleware that significantly simplifies the creation of distributed systems.

Preliminary experiments on mammograms restricted to normals and masses suggest that the use of this search engine will enhance the reliability and accuracy of the diagnosis of breast cancer. In addition the relational map provides a means of discovering image relationships that may lead to improved diagnosis. The relational map may also assist in the training of radiologists.

7. **KEYWORDS:** teleradiology, digital mammography, computer-aided diagnosis, region of interest, digital library, content-based retrieval

8. **BRIEF BIOGRAPHY OF CHESTER ORNES:**

Chester Ornes received a BSEE degree from the University of California at Santa Barbara in 1980 and an MSEE degree from the University of California at Irvine in 1997. He has published seven papers on computer-aided diagnosis and neural classifiers. He has over fifteen years of experience as a system engineer in electronics, machine vision, and machine learning. He worked for four years with the Pattern Recognition and Image Modeling Laboratory at the University of California at Irvine. He recently began collaborating with the Medical Informatics Laboratory at the University of California at Los Angeles. He is the principal system engineer for the Digital Mammography project at the Charles R. Drew University of Medicine & Science.



Example of a relational map. In this map each malignant ROI is labeled **X**, and each benign ROI is labeled **o**. The query ROI is labeled **■**.

FIGURE FOR PAPER SUBMITTED TO: mi05 Siegel, Huang

TITLE OF CONFERENCE: PACS and Integrated Medical Information Systems: Design and Evaluation

PAPER TITLE: A search engine for remote database-aided interpretation of digitized mammograms.

PRINCIPAL AUTHOR: Chester J. Ornes

APPENDIX 3.

Form for mammographic assessment and findings; list of pathology codes.

MAMMOGRAPHY ASSESSMENT AND FINDINGS

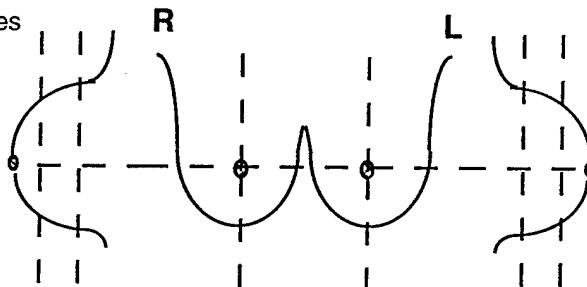
Patient Study Identification Number	Age	Date	
Screening Assessment	Oa Ou Oo	1 2 3 4 5	
Final Assessment	1 2 3	4a 4b 4c 5	
Breast Composition	1 2 3	4	
Clinical Correlation	Finding correlates to clinical exam finding in <input type="checkbox"/> L <input type="checkbox"/> R <input type="checkbox"/> B breast(s) at _____ o'clock		

Assessment Categories

Oa = Additional films
 Ou = Ultrasound
 Oo = Outside Films
 1 = Negative
 2 = Benign finding
 3 = Probably benign
 4 = Suspicious abnormality (a-mild, b-moderate, c-high)
 5 = Highly suggestive of malignancy

Breast Composition

1 = Almost entirely fat
 2 = Scattered fibroglandular densities
 3 = Heterogeneously dense
 4 = Extremely dense

Mammography Findings

MASS

Size /Number	In area of density?	Shape	Margins	Density	
				cm	#
_____ cm	_____ #	<input type="checkbox"/> Yes <input type="checkbox"/> Round <input type="checkbox"/> Lobular <input type="checkbox"/> No <input type="checkbox"/> Oval <input type="checkbox"/> Irregular	<input type="checkbox"/> Circumscribed <input type="checkbox"/> Ill-defined <input type="checkbox"/> Microlobulated <input type="checkbox"/> Spiculated <input type="checkbox"/> Obscured	<input type="checkbox"/> High <input type="checkbox"/> Low	<input type="checkbox"/> Equal <input type="checkbox"/> Fat containing
_____ cm	_____ #	<input type="checkbox"/> Yes <input type="checkbox"/> Round <input type="checkbox"/> Lobular <input type="checkbox"/> No <input type="checkbox"/> Oval <input type="checkbox"/> Irregular	<input type="checkbox"/> Circumscribed <input type="checkbox"/> Ill-defined <input type="checkbox"/> Microlobulated <input type="checkbox"/> Spiculated <input type="checkbox"/> Obscured	<input type="checkbox"/> High <input type="checkbox"/> Low	<input type="checkbox"/> Equal <input type="checkbox"/> Fat containing

CALCIFICATIONS
Distribution Modifiers

- Grouped/Clustered
- Linear
- Segmental
- Regional
- Diffuse/Scattered

Typically Benign

- Skin
- Vascular
- Coarse
- Large rod-like
- Round
- Lucent-centered
- Eggshell/Rim
- Milk of Calcium
- Suture
- Dystrophic
- Punctate

Intermediate Concern

- Amorphous or Indistinct
- Higher Probability of Malignancy**
- Pleomorphic/heterogeneous
- Fine, linear branching

Other Findings

- Skin thickening
- Trabecular thickening
- Skin lesion

- Skin retraction
- Nipple retraction
- Axillary adenopathy

- Asymmetric breast tissue
- Focal asymmetric density
- Architectural distortion

Pathology Diagnosis: Benign _____ Malignant _____

Comments:

MAMMOGRAPHY PATHOLOGY CODES

MALIGNANT		BENIGN	
ANC	metastatic disease Axillary Node	AB	ABscess
CC	Colloid (mucinous) Carcinoma	AD	ADenosis
CI	Comedocarcenoma (Intraductal)	ANL	Axillary Node with Lymphoma
CP	intraCystic Papilloma	BC	Benign Cyst
DS	Ductal carcinoma in Situ	DE	Duct Ectasia
IC	Intracystic papillary Carcinoma	DH	Ductal Hyperplasia
ID	Invasive Ductal carcinoma	EC	Epidermal inclusion Cyst
II	Invasive and In situ cancer	FA	FibroAdenoma
IL	Invasive Lobular carcinoma	FB	Foreign Body
IN	INflammatory carcinoma	FC	FibroCystic change
IP	Papillary Invasive carcinoma	FF	Focal Fibrosis
LN	Lymph Node	FN	Fat Necrosis
LY	Lymphoma	GA	GAlectocele
MB	Metastatic lesion to the Breast	GF	Giant Fibroadenoma
MC	Medullary Carcinoma	GYN	GYNecomastia
MI	Multifocal Intraductal carcinoma	HB	Hamartoma of the Breast
PC	Papillary Carcinoma in situ	HE	Hematoma
PD	Paget's Disease	IM	IntraMammary node
RM	Recurrent Malignancy	LB	Lipoma of the Breast
S	Sarcoma	LH	Lobular Hyperplasia
TC	Tubular Carcinoma	LN	Lymph Node
HIGH RISK LESIONS			
ATD	ATypical Ductal hyperplasia	LP	Large duct Papilloma
ATL	ATypical Lobular hyperplasia	NA	No Abnormality
LS	Lobular carcinoma in Situ	PT	Phylloides Tumor
PP	Peripheral duct Papilloma	RS	Radial Scar
		SA	Sclerosing Adenosis
		SE	SEroma
		SG	Silicone Granuloma
		ST	Scar Tissue

APPENDIX 4

Research protocol for database-aided telemammography.

IRB #:45

PII Redacted

Charles R. Drew University Institutional Review Board
Application for Study Review¹

I. Project Information

1. Project Title: <i>(Use exact title of grant or contract, as applicable)</i>	DATABASE-AIDED TELEMAMMOGRAPHY		
<i>If this research is being submitted to or supported by an extramural funding, the PI listed on the grant must match the PI listed below. Please list the address and telephone number where the PI may be most easily reached. If the PI is completing this project to meet the requirements of an academic program, also list the name and address of the faculty sponsor.²</i>			
2. Principal Investigator:	Jack Sklansky, Eng. Sc.D.		
Telephone Number:	310-668-4743	Fax Number:	310-631-4763
E-Mail Address:	sklansky@uci.edu		
3. Co-Investigator or Faculty Sponsor	Jack I. Eisenman, MD		
Telephone Number:	310-668-4701	Fax Number:	310-632-8068
E-Mail Address:	jeisenma@ucla.edu		
4. Co-Investigator #2			
Address:			
Telephone Number:			Fax Number:
E-Mail Address:			
5. Primary Contact Person:	Jack Sklansky, Eng.Sc.D.		

II. Investigator's Assurance

The Principal Investigator must assure the Board that all procedures performed under the project will be conducted in strict accordance with all applicable federal, State and local regulations and laws regarding the protection of human subjects in research including, but not limited to:

1. Use of qualified personnel to conduct the project according to the protocol approved by the IRB
2. Ensuring that no changes are made to the approved protocol or consent form without prior IRB approval (except in an emergency to safeguard the well-being of subjects)
3. Using the most current, approved, stamped consent form to obtain informed consent from subjects or their legally responsible representative
4. Prompt reporting of significant adverse events (AEs) to the IRB in writing within 5 working days of occurrence (within 24 hours for serious AEs)
5. If I will be unavailable to direct this research personally, as when on leave or vacation, I will arrange for a co-investigator to direct responsibility in my absence. If this is not the co-investigator named absence, I will notify the IRB in writing of the responsible party.

Signature of Principal Investigator

4-19-01

Date

CHARLES R. DREW UNIVERSITY
 IRB COMMITTEE APPROVED
 DATE: APR 20 2001
 VOID AFTER APR 19 2002

¹ Includes Applications for Re-review² If there are additional Investigators, please attach additional sheets.

III. Faculty Sponsor's Assurance

By my signature as sponsor on the research application, I certify that the student is knowledgeable about the regulations and policies governing research with human subjects and has sufficient training and experience to conduct this particular study in accord with the approved protocol. In addition,

1. I agree to meet with the investigator on a regular basis to monitor study progress.
2. Should problems arise in the course of the study, I agree to be available to personally supervise the investigator in solving them.
3. I assure that the investigator will promptly report AEs to the IRB according to the schedule indicated above.
4. If I will be unavailable, as on vacation, I will arrange an alternate faculty sponsor to assume responsibility during my absence and I will advise the IRB of such arrangements.

Faculty Sponsor (if PI is a student, resident, or fellow)

Date

**IV. Funding**

Federal Pharmaceutical Company Private Foundation Internal grant program, Industry,
 Other, Specify:

Funding Source:	California Telehealth & Telemedicine Center
-----------------	---

Contract or Grant Title*:	Database-Aided Telemammography
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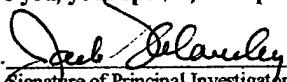
Contract or Grant #:	221
----------------------	-----

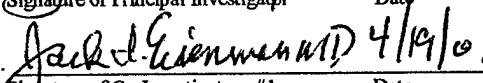
*Please indicate whether the study under review is being conducted under the auspices of a larger umbrella grant (e.g., RCMI Clinical Research Center, Program Project Grant)

 Yes No**V. Statement of Financial Interests**

By their signatures below, each investigator is certifying that either no financial interest exists or that a complete listing of all financial interests related to the proposed project is provided. All individuals named below further acknowledge their responsibility to disclose any new reportable financial interest obtained during the term of the project. The Principal Investigator's signature also certifies that all individuals required to make disclosures have been listed below:

Do you, your spouse, or dependent children, have a financial interest in the work to be conducted under the proposed project?

1.  4-19-01 NO YES, Attach Financial Disclosure Form
 Signature of Principal Investigator Date

2.  4/19/01 NO YES, Attach Financial Disclosure Form
 Signature of Co-Investigator #1 Date

3. _____ NO YES, Attach Financial Disclosure Form
 Signature of Co-Investigator #2 Date

VI. Application Status:

6. Please check the appropriate description of the study:

New Application (go to Section VII) Re-review of study previously approved by full IRB
 Re-review of study previously approved by expedited review,
 Re-review of study previously judged to be exempt

7. Date of Original Review	
----------------------------	--

8. Date(s) of continuation reviews	
------------------------------------	--

9. Total number of subjects anticipated to be enrolled	1200
--	------

10. Total number of subjects enrolled to date	0
---	---

11. Age range of subjects	18 and over
---------------------------	-------------

12. Is this study permanently closed to new subject enrollment?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
---	---

13. Have you completed the data analysis?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
---	---

Note: As long as data analysis is being conducted, this study will remain open with the IRB

14. Have there been any unexpected reactions or complications during the conduct of this study? If so, please attach adverse event reports.	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
--	---

VII. Summary Information					
1. Has a Data Safety Monitoring Board been established to review data/adverse events related to this study?				<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2. Subject Population (please check all appropriate boxes)					
<input type="checkbox"/> a. Abort uses/fetuses	<input type="checkbox"/> e. Drew House Officers/Residents ¹	<input type="checkbox"/> i. Normal volunteers	<input type="checkbox"/> m. Students		
<input type="checkbox"/> b. Cancer subjects	<input type="checkbox"/> f. Elderly	<input checked="" type="checkbox"/> j. Patients	<input type="checkbox"/> n. Terminally ill		
<input type="checkbox"/> c. Comatose	<input type="checkbox"/> g. Institutionalized	<input type="checkbox"/> k. Prisoners or parolees	<input type="checkbox"/>		
<input type="checkbox"/> d. Decisionally impaired	<input type="checkbox"/> h. Minors	<input type="checkbox"/> l. Pregnant women	<input type="checkbox"/>		
¹ Approval of Graduate Medical Office is necessary prior to IRB approval					
3. If the research involves any of the following, check the appropriate boxes					
<input type="checkbox"/> a. Audio/videotapes	<input type="checkbox"/> m. HIV screening				
<input type="checkbox"/> b. Acute care waiver of informed consent	<input type="checkbox"/> n. Investigational drugs				
<input type="checkbox"/> c. Alcohol and drug abuse research	<input checked="" type="checkbox"/> o. Investigational devices				
<input type="checkbox"/> d. Behavioral observations	<input type="checkbox"/> p. Multicenter clinical trial ²				
<input type="checkbox"/> e. Biohazardous waste	<input type="checkbox"/> q. Magnetic Resonance imaging				
<input type="checkbox"/> f. Collection of biological specimens for banking	<input type="checkbox"/> r. National Cancer Institute Trial (NCI) ³				
<input type="checkbox"/> g. Collection of surgical specimens	<input type="checkbox"/> r. NIH Cooperative Groups (i.e., RCMI)				
<input type="checkbox"/> h. Controlled substances	<input type="checkbox"/> s. PI or co-PI is the treating clinician				
<input type="checkbox"/> i. Deception	<input type="checkbox"/> t. Radiation				
<input type="checkbox"/> j. Gene therapy	<input type="checkbox"/> u. Surveys, questionnaires, psychological testing				
<input type="checkbox"/> k. Genetic research	<input type="checkbox"/> v. Transplantation				
<input type="checkbox"/> l. HIV/AIDS	<input type="checkbox"/> w. Vaccine trials				
² If the research is part of an NIH multi center clinical trial, the NIH sample informed consent form must be included with the submission. ³ For trial sponsored by NCI, all approved changes must be forwarded to the Cooperative Group Headquarters.					
4. If the research is to be conducted at any other site than the CRDUMS or the KDMC, check all that apply.					
<input type="checkbox"/> a. Harbor General Hospital	<input type="checkbox"/> f. USC/LA County Medical Center				
<input type="checkbox"/> b. UCLA Medical Center	<input type="checkbox"/> g. Cedars/Sinai Medical Center				
<input type="checkbox"/> c. St. Francis Medical Center	<input type="checkbox"/> h. Daniel Freeman Medical Center				
<input checked="" type="checkbox"/> d. Other hospital or medical center, specify: Hubert H. Humphrey Comprehensive Health Center (HHHCHC)					
<input type="checkbox"/> e. Other facilities, specify:					
Note: If any offsite facilities are indicated, IRB approval and a letter of support for this protocol are required from that institution. If the site does not have an IRB, it may be necessary to obtain a Single Project Assurance from OPRR to conduct the study at that site. Please check with the IRB office.					
5. If there are any investigational drugs or biologic agents used in this study, please complete and include the Investigational Drug Information Form with this application.					
6. Will you be using the Clinical Research Facilities?					
7. Does your protocol require review by the Radioactive Drug Research Committee? <i>If yes, please indicate the date of approval or if approval is pending:</i>					
8. Does your protocol require review by the Biohazards and Safety Committee? <i>If yes, please indicate the date of approval or if approval is pending:</i>					
9. Is this research being conducted to meet requirements for a course or to complete an academic degree?					
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No					
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No					
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No					
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No					

VII. Protocol Summary

Please fill out the information requested in the following categories. If the item does not apply to your research, simply indicate that the question is not applicable. The information should be intelligible to IRB reviewers from a variety of lay and scientific backgrounds.

1. Purpose of the study: What are the specific scientific aims of this study?

A digital telemammography system linking the Hubert H. Humphrey Comprehensive Health Center (HHHCHC) to the "mapped database diagnostic system at the King/Drew Medical Center (KDMC) will be designed, installed, operated, and evaluated. We wish to demonstrate that the proposed database-aided telemammography system will enable a significant reduction in recalls and biopsies without reducing the number of missed cancers. Statistics on the use of this system will be acquired over the period of this project to assist in evaluating its impact on the quality of mammographic services at HHHCHC.

2. Background: State the background of the study, including a critical evaluation of existing knowledge and the information gaps that this research proposes to fill. Describe previous work that provides a basis for the proposed research and that supports the expectations of obtaining useful information without undue risk to human subjects. Please include relevant citations.

Professor Jack Sklansky, in the Department of Radiology at C.R. Drew University, recently supervised the development of a major new concept for computer-aided diagnosis: mapped-database reasoning. A pilot mapped-database diagnostic system was tested successfully at Drew for the diagnosis of apparent calcifications in digitized mammograms. This system currently uses a database of over 1000 full-field digital mammograms, along with marked regions of interest (ROIs). The database was acquired from the University of South Florida. A neural network maps this database onto a two-dimensional display. The network does this by mapping each ROI into a dot on a screen, and arranges the dots so that they cluster into visually and medically similar groups. By annexing this neural network to a means of quickly retrieving and viewing ROIs that are mapped close to query ROI, the radiologist is given a simple way of conversing with the database to enhance the reliability of the radiologist's diagnostic decisions. Preliminary tests suggest that the mapped-database diagnosis can reduce the number of biopsies by about 40% without increasing the number of missed breast cancers. Such reductions could bring significant financial and operational efficiencies to the detection and diagnosis of breast cancer.

3. Study Design: Describe the study design (e.g., double blind, crossover, etc.) and sequentially list all procedures, drugs or devices to be used on human subjects. Describe any use of placebos and indicate whether subjects will be randomized in this study. If there are any investigational drugs or biologic agents used in this study, please complete and include Attachment #1 with this application.

The project will extend over a one-year period. During the first two months, the scanning and computing hardware and the communication software will be installed and tested. Radiologists participating in this study will be trained in the use of the mapped-database system as a diagnostic aid. During the remaining ten months of this project, data will be accumulated on the speed and diagnostic accuracy of both the standard procedure for mammographic diagnosis and the remote-access database-aided mammographic diagnosis. On two days of each week, all of the mammography patients arriving at HHHCHC will be invited to enroll in this study. Those that do not accept this invitation will be examined by the standard diagnostic procedure currently carried out at HHHCHC ("standard procedure," for short). Each subject that accepts the invitation will first be examined by the standard procedure. The resulting diagnosis by the radiologist (which we refer to as the "standard diagnosis") and other pertinent data for this subject will be entered into the study's subject database. At that point the computer will randomly decide whether or not for this subject the standard diagnosis will be followed by a database-aided diagnosis. If the subject is selected for a database-aided diagnosis, the radiologist will interact with the computer to form a database-aided diagnosis for this subject. This diagnosis will be added to the computer's file for this subject. In all cases the standard diagnosis will determine the management of the subject. However, as a result of the radiologist's interaction with the computer and its database of similar cases, the radiologist may decide to recall the subject to discuss options and advisability for further tests and procedures.

Study Population
4. Study Population: Describe the characteristics of the subject population such as the anticipated number, age range, gender, ethnic background and health status. Provide a candid discussion of potential problems related to the study population. Explain the rationale for the use of special classes such as fetuses, pregnant women, children, prisoners, or other vulnerable populations. If women, minorities or children are excluded, provide written justification.
The subject population will be restricted to all women at least 18 years old requesting mammography at HHHCHC. The expected number of subjects entering this study is about 1200. The ethnic background will reflect the population served by HHHCHC: primarily African-American and Latino.
5. Indicate the criteria for exclusion and inclusion and explain the system for equitable selection of subjects. Any woman at least 18 years old who is accepted for standard mammography at HHHCHC will be eligible for this study.
6. How is eligibility determined and by whom? Research associates will accept to this study all female <u>subjects</u> at least 18 years old and receiving standard mammographic care at HHHCHC.
7. Recruitment: What methods will be used to identify and recruit potential subjects. Attach a copy of all planned advertisements, flyers and letters, etc. to potential subjects. Subjects for this study will be recruited from those arriving for mammography in the radiology waiting room at HHHCHC. On two days of each week, a research associate trained for this project will wait for mammographic patients arriving in the radiology waiting room. The research associates for this study will be Ricardo Vega, M.D. and La Tasha Peterson. Dr. Vega will be responsible for interviewing and recruiting the subjects for this study. La Tasha Peterson will assist him. Dr. Vega or Ms. Peterson will carry out each recruitment interview. The receptionist in the radiology waiting room will ask the potential subject whether she would be interested in learning about an ongoing clinical research project. If the potential subject says Yes, the receptionist will introduce the potential subject to either Dr. Vega or Ms. Peterson.

Research Methods and Procedures

- 8. Methodology and Data Collection:** Describe the research procedures that will be followed. Please indicate those that are experimental and those that may be considered to be standard treatment. Describe all activities involving human subjects and explain the frequency and duration of each activity.

Using the subjects' film mammograms and medical histories we will compare two modes of mammographic diagnosis from the points of view of health benefits and speed. These modes are listed below.

Mode A: reading of film-screen mammograms at HHHCHC, with no computer-aided diagnosis. We refer to this as "standard" mammographic diagnosis. This diagnosis will determine the management of the subject for Mode A.

Mode C: reading of film-mammograms at HHHCHC, with the use of the remotely sited computer as an aid to diagnosis. We refer to this as "database-aided" mammographic diagnosis.

Mode C will consist of two parts in succession: C1 followed by C2. In C1 the radiologist will read the films as in Mode A, with no computer-aided diagnosis. This diagnosis will determine the management of the subject for Mode C. In C2 the radiologist will interact with the database-aided diagnostic system to formulate a possibly revised diagnosis. As a result of this interaction, the radiologist may decide to recall the subject to discuss options and advisability for further tests or procedures.

The assignment of each subject to either Mode A or Mode C will be carried out by a computer-generated random process immediately after completion of the standard mammographic diagnosis for that subject.

In A, C1, and C2, the responsible radiologist will score each subject by the BI-RADS code (1=normal, 2=benign, 3=probably benign, 4=suspicious, 5=probably malignant). For each subject the recorded data will include a) the date and time of arrival of each mammography subject, b) the responsible radiologist, and c) the date and time when the treatment, if any, of that subject is determined.

At the end of the acquisition of data for this study, the speed and diagnostic effectiveness of the mammographic services provided by Modes A and C will be evaluated. This evaluation will be based on analysis of the recorded data in Modes A and C and on interviews with the radiologists at HHHCHC that are involved with this study.

- 9. If your study uses surveys, questionnaires, or psychological tests, please describe the provisions for administering these measures, the mode of administration, the setting and if special training or qualifications are necessary.**

10. Please complete the following questions regarding data storage:

<p>a. How will the data be collected and recorded? How will the data be coded to protect personal privacy?</p>	<p>Mammographic data will be sent to KDMC and back to HHHCHC. Before transmittal to KDMC, each subject's name will be deleted. A numeric tag will identify the data but not the person. The resulting tagged images will not be identifiable to anyone outside of the Department of Radiology at HHHCHC.</p>
<p>b. How will the data be stored during the study?</p>	<p>The depersonalized data will be stored in our computer's memory at KDMC. All personal identifiers will be deleted from this data. In addition, the personalized data will be stored in a locked file cabinet at HHHCHC. The personalized data will be accessible only to the subject's radiologist or to another medical professional approved by the subject.</p>

c. Who will have access to the data and the data codes? If data with subject identifiers will be released, specify the person(s) and agencies to whom this information will be released	The principal investigator, the computer engineer, and radiologists from KDMC and HHHCHC will have access to the depersonalized data. The personalized data will be accessible only to the subjects; radiologists at HHHCHC or to another medical professional approved by the subject.
d. What will happen to the data when the study is completed?	The data at KDMC with personal identifiers deleted will remain intact, and will be available for use in future research. The personalized data will be under control of the subject and the subject's radiologist.

Risk/Benefit Assessment

11. Potential Risks and Discomforts: Describe any potential risks or likely adverse effects of the drugs, biologics, devices or procedures subjects may encounter in the study. State the potential risks – physical, psychological, social, legal or other – connected with the proposed procedures and assess their likelihood and seriousness.

There are no serious risks in taking part in this research. The subject may be called back by the radiologist for additional workups or biopsies as a result of enhancement of the radiologist's diagnostic ability provided by the digitized database.

12. Risk Classification: Please check the level* of risk associated with this study

* According to HHS/FDA regulations minimal risk means, "The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." When the risks that are associated with a new procedure or product are unknown, they cannot be classified as minimal.

minimal greater than minimal unknown

13. Safety Precautions for Minimizing Risks: Describe the procedures for minimizing any potential risks. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects to the subject. Where appropriate describe the provisions for monitoring the data collected to ensure the safety of the subjects.

The radiological risks are the same as in ordinary screening or diagnostic mammography.

14. Benefit Ratio: What is the risk benefit ratio of this research, compared with available alternatives? Describe the potential benefits the subjects may receive as a result of their participation in the research and what benefits to society may be expected. The potential benefits of the research must justify the risks to human subjects. The risk benefit ratio of the research must be at least as favorable for the subjects as that presented by standard treatments for their condition. When comparing the risk/benefit ratio of research with that of available alternatives, the alternative of doing nothing should be included in the analysis.

15. Therapeutic Alternatives: What therapeutic alternative(s) are reasonably available to potential subjects should they choose not to participate in the study? These may be research or non-research-based alternatives.

There are no therapeutic alternatives to this project. If the subject does not wish to participate in this study, she will receive a standard mammographic examination that does not involve computer-aided diagnosis.

Financial Considerations

16. Payment for Participation: Describe all plans to compensate subjects, including provision of services, and other reimbursements. Describe the conditions that subjects must fulfill to receive full or partial payment.

Each subject will be paid ten dollars for participating in this project. Subjects will not receive any financial compensation for any commercial product created as a result of this project.

17. Financial Obligations of Subjects: Will subjects have to pay for any of the tests or treatments that they receive as part of the research? Please clarify who will pay for the procedures associated with the study as well as procedures that may be part of standard clinical care. Clarify that insurance and other third party payors may not cover standard procedures if they are associated with a research project.

Subjects will not incur any financial obligations as a result of participation in the study other than the fees HHCHC usually charges for a mammogram.

18. Emergency Care and Compensation for Research-Related Injury: If the research presents a greater than minimal risk, the financial liability for the costs of care associated with potential research related illness/injury must be specified. (if no funds are available, please see the consent form template for the standard language to explain this to potential subjects)

This study does not present greater than minimal risk. Subjects will not be compensated for out-of-pocket expenses or lost wages if they suffer a research related injury.

Informed Consent

19. Capacity to Consent: Will all subjects have the capacity to give informed consent? If not, describe the likely range of impairment and explain how, and by whom, their capacity to consent will be determined.

Adult subjects will have the capacity to give informed consent.

20. Study Personnel Administering the Consent Process: Please identify by name and training the individual(s) who will be authorized to describe the research to subjects, or their representatives, and to invite their participation. To insure that subjects give complete informed consent and are able to ask and have answered all questions regarding the nature of their participation, the personnel administering the consent must have appropriate training and background.

Ricardo Vega, M.D., assisted by La Tasha Peterson, will be authorized to read and explain the contents of the Human Subject Consent Form to each subject. Dr. Vega is a member of Drew's RCMI, and has extensive experience in interacting with human subjects in clinical research. La Tasha Peterson is the Program Administrator of Dr. Sklansky's research project on database-aided mammographic diagnosis. Dr. Vega and Ms. Peterson will be trained for this project in Dr. Sklansky's laboratory at KDMC. Both Dr. Vega and Ms. Peterson successfully completed a course on Protection of Human Subjects.

21. Process of Consent: Please discuss how the consent process will be conducted, describing the following elements: a) the environment and location where the informed consent will be solicited; b) opportunities for the potential subjects to discuss their participation with family or others before signing the consent form; c) how and by whom it will be determined whether the subject or their legally authorized representatives understand the information provided; and d) the types of forms used (e.g., adult consent form, assent form for youth, translations to other languages, etc.)

The subjects will have as much time as they wish to study the consent form alone or with family members, and to ask questions of the radiology staff before signing the form. The radiologists and radiological staff will be trained to avoid any semblance of psychological pressure on the subject while presenting and explaining the consent form.

22. Information Withheld from Subjects: Will any information about the research purpose and design be withheld from subjects? If so, please explain the non-disclosure and describe plans for post-study de-briefing.

None of this information will be withheld.

Data Analysis

23. Please delineate the data analysis plans for this study. Include planned statistical analyses and explanation of determination sample size.

For details on data analysis, see section 8 on "Methodology and Data Collection."

APPENDIX 5

Abstract of *infoRAD* 2000 exhibit.

ABSTRACT

DATABASE-AIDED DIGITAL MAMMOGRAPHY

by

J. Sklansky, EngScD and C. J. Ornes, MS

infoRAD Exhibit

**presented at the 2000 Annual Meeting
of the Radiological Society of North America
November 26-December 1, 2000
Chicago, Illinois**

We demonstrated a new system for the database-aided diagnosis of mammograms. This system includes two computers, a scanner, two high-resolution monitors, and two standard computer monitors. In this system a recently devised "visual neural network" maps each region of interest (ROI) in a database of proven mammographic ROIs as a dot on one of the monitors. We refer to this array of dots as a relational map. Clusters of dots on the relational map represent visually similar ROIs. For each new case to be analyzed, a dot representing the query ROI is superimposed on the relational map. The radiologist is then given an opportunity to use the relational map to search for similar ROIs from a database of proven ROIs. In addition to creating the relational map the neural network responds to a query ROI by recommending either to biopsy or not to biopsy. Preliminary results suggest that providing a radiologist with a neural network "second opinion" and allowing the radiologist to browse a database of ROIs may lead to a reduction in the number of benign biopsies without an increase in the number of missed cancers.

CERTIFICATE OF MERIT

The Radiological Society of North America awarded each of the authors a Certificate of Merit "in recognition of the excellence of your *infoRAD exhibit*."

APPENDIX 6

Curriculum Vitae of Jack Sklansky, EngScD.

CURRICULUM VITAE

[PII Redacted]

Name: Jack Sklansky

[REDACTED]

[REDACTED]

Education: Eng.Sc.D., 1955, Columbia University
M.S.E.E., 1952, Purdue University
B.E.E., 1950, The City College of New York

Honors and Awards:

Fellow of the Institute of Electrical and Electronics Engineers
Fellow of the International Association for Pattern Recognition
Award for Research Excellence, School of Engineering, UCI
Annual Award of the Pattern Recognition Society
Tau Beta Pi
Sigma Xi
Eta Kappa Nu
Who's Who in America

Professional Interests:

Automatic pattern recognition, machine vision, medical imaging, computer-aided diagnosis, intelligent machines, trainable classifiers, learning theory, neural networks, computer engineering, biomedical engineering.

Academic Appointments:

Research Professor of Electrical and Computer Engineering and of Radiological Sciences, University of California, Irvine, 1994-present

Professor of Radiology, Charles R. Drew University of Medicine and Science, 1996-present

Research Professor of Radiological Sciences, UCI, 1971-1994

Professor of Electrical and Computer Engineering, UCI, 1969-1994

Professor of Information and Computer Science, UCI, 1969-1989

Chairman of Electrical Engineering: 1978-1979

Associate Professor of Electrical Engineering, UCI, 1966-1969

Consulting Activities since 1987:

CR Technology, Laguna Niguel, California, 1997- present
Member of Board of Directors of Vartec Corporation, Irvine, California, 1984-1992.
Synthetic Aperture Real Time Imaging Corporation, 1991
Carelink, 1990
De La Rue Printrak, 1990
Curt Decker Associates, 1990
U. S. Army, 1988
John Wiley and Sons, 1988
Addison Wesley, 1988
Aerojet-General 1988

Honors and Awards:

Fellow of the Institute of Electrical and Electronics Engineers, for contributions to digital pattern classification and medical applications.”

Fellow of the International Association for Pattern Recognition, “for contributions to pattern recognition, machine, and medical imaging, and service to the IAPR.”

Award for Research Excellence, School of Engineering, UCI
Annual Award of the Pattern Recognition Society
Tau Beta Pi
Sigma Xi
Eta Kappa Nu
Who's Who in America

Professional Service and Activities:

Member of Advisory Committee for
MTAC 2000 – The Multimedia Conference for the Arts and Sciences

Chair of Welfare Committee of UCI Emeritae/I Association

Co-Chair of International Workshop on Digital Video for Intelligent Systems,
December 1993.

Member of Governing Board of the International Association of Pattern Recognition
(IAPR)

Chairman of the IAPR King-Sun Fu Award Committee

Member of Editorial Board of *Machine Vision and Applications*

Associate Editor of *Pattern Recognition*

Co-editor of Special Issue of the Journal of the Optical Society of America A on "Pattern Recognition and Image Understanding"

Member of Organizing Committee and Program Co-Chairman of the International Symposium on Computer-Aided Radiology, held in Anaheim, California in June 1990.

Member of Organizing Committee of the 1990 International Symposium on Computer-Assisted Radiology.

Member of Program Committee of the Third Int. Conf. on Computer Analysis of Images and Patterns, Leipzig, German Democratic Republic, September 1989

Member of Program Committee of 1989 International Symposium on Computer-Assisted Radiology, June 1989

Member of Adv. Board of IEEE Trans. on Pattern Analysis and Mach. Intelligence.

Co-chairman of U.S. Army Conference on Pattern Recognition in Advanced Missile Systems, Huntsville, Alabama, November 1988.

Co-chairman of Program Committee for SPIE Conference on Hybrid Image and Signal Processing, Orlando, Florida, April 1988.

Session chair at the following conferences since 1987:

Pattern Recognition in Practice, June 1997

International Conference on Pattern Recognition, August 1996

International Conference on Computer Analysis of Images and Patterns, Sept. 1993.

International Conference on Pattern Recognition, September 1992

International Conference on Pattern Recognition, June 1990

International Symposium on Computer-Assisted Radiology, June 1989

International Conference on Computer Analysis of Images and Patterns, September 1989

International Conference on Pattern Recognition, November 1988

Conference on Pattern Recognition in Advanced Missile Systems, November 1988

SPIE Conference on Hybrid Image and Signal Processing, April 1988

Reviewer for the following journals:

IEEE Transactions on Pattern Analysis and Machine Intelligence

Machine Vision and Applications

IEEE Transactions on Medical Imaging

Pattern Recognition

Computer Vision, Graphics and Image Processing

International Journal of Pattern Recognition and Artificial Intelligence

IEEE Transactions on Systems Man and Cybernetics

Journal of the Optical Society of America A

Reviewer for the following funding agencies:

National Science Foundation

National Institutes of Health

U.S. Army Research Office

University of California MICRO program

National Research Council of Canada

Reviewer of books for the following publishers:

IOP Publishing Ltd., Philadelphia

Springer-Verlag, New York

John Wiley, New York

Addison-Wesley, Reading, Massachusetts

Ph. D. Advisees: (names, title of dissertation, year of graduation, current position if known)

Brian Lofy, "Segmenting and Matching of Aerial Images Acquired by Different Sensors," 1999: Senior Engineer, Marconi Integrated Systems, San Diego, California.

Eric Y. Tao, "Database-Aided Diagnosis in Digital Mammography," 1998: Assistant Professor, Institute of Communication Science and Technology, California State University, Monterey Bay, California

Mark Vriesenga, "Genetic design of pattern classifiers," 1995: Senior Engineer, GDE Systems, San Diego, California.

L.V. Tran, "Quantitative Biplane Angiography", 1991: Research Engineer, Northrop Corporation, Anaheim, California

Y. Moon, "Multicomputer architectures for image analysis," 1990: Assistant Professor, Korea Academy of Industrial Technology, Seoul, Korea

D. Gutfinger, "Mixed Adaptation -- a Theory for Designing Robust Classifiers," 1990: Student at UCI College of Medicine

Y. Park , "Linear Tree Classifiers" 1990, Assistant Professor, Kyung Hee University, Suwon Campus, Yongin, Kyungkido, Korea

W. W. Siedlecki, "Feature selection for large scale classifiers," 1988: Vice President for Research, P-Logic Corporation

K. Kitamura, "Estimating the transverse areas and boundaries of coronary arteries in three dimensions," 1987: Research Engineer, Nippon Steel Corporation

P. E. Chandler, "A multiple scattering model for pulse propagation within velocity inhomogeneous, lossy, and refractive media," 1986

T. V. Nguyen, "Three-dimensional reconstruction of the medial axes of coronary arteries from single-view angiograms," 1986: President, Multisignal Technology Corporation; Professor, California State University, Long Beach, California

I. Foroutan, "Feature selection for piecewise linear classifiers," 1985: Manager of Circuit Automation, Hughes Aircraft Co.

M. Hashimoto, "Estimation of multiple-order derivatives for edge detection," 1984: member of Japan Defense Force

D. Petkovic, "A computer system for coarse-fine detection of pulmonary nodules in chest radiographs," 1983: Manager of Department of Advanced Algorithms, Architectures, and Applications, IBM Almaden Research Center

L. A. Ferrari, "Recursive binary-valued image filters," 1980: Associate Professor of Electrical and Computer Engineering, Chairman of Department of Electrical and Computer Engineering, UC Irvine

E. J. Pisa, "Computing the geometry of the rib cage from two chest radiographs," 1979: Vice President of Research and Development, Ivac Corporation

H. Wechsler, "Automatic Detection of Rib Contours in Chest Radiographs," 1975: Professor of Computer Science, George Mason University

D. H. Ballard, "Hierarchic Recognition of Tumors in Chest Radiographs," 1974: Professor of Computer Science, University of Rochester

P. J. Nahin, "A parallel machine for describing and classifying silhouettes," 1972: Associate Professor of Electrical Engineering, University of New Hampshire

P. M. Merryman, "Dynamics of multidimensional Markov learning," 1972: Senior System Engineer, Ultrasystems, Inc.

G. N. Wassel, "Training a linear classifier to optimize the error probability," 1972: Professor of Electrical Engineering, Cal Poly University, San Luis Obispo, California

H. R. Ramanujam, "A stopping rule for threshold learning," 1970: Principal Engineer, McDonnell Douglas Corp.

M. S. Advisees:

Chester J. Ornes, "A Neural Classifier for Database-Aided Decisions," 1997.

J. Ribas-Corbera, "Image Data Compress and Interframe Interpolation of Cinematic Sequences," 1992.

M. R. Vriesenga, "Colored Illumination for Maximizing Contrast in Machine Vision," 1991.

R. Agarwal, "Optical Flow from Clusters in Velocity Space," 1991.

E. M. Hertzberg, "Quantitative Analysis of Magnetic Resonance Images," 1991.

- J. B. Bartels, "Analysis of Random and Systematic Errors in T_1 Measurement with Gradient Echo Magnetic Resonance Imaging," 1990.
- S. R. Reuman, "Computing Albedo, Illumination, and Optical Flow with Spacetime-Adaptive Bandpass Filtering," 1988.
- J. J. Duffy, "Time Varying System Feedback Design," 1988.
- N. Iliev, "Failure Isolation in Linear Stochastic Systems -- the Associative Recall Approach," 1987.
- R. F. DeShetler, "Finding the Polyhedra Formed by the Hyperplanes of a Piecewise Linear Classifier," 1986.
- N. P. DeMesa, "Petri Net Analysis," 1986.
- P. E. Chandler, "A Multiple Scattering Model for Pulse Propagation within Velocity Inhomogeneous, Lossy, and Refractive Media," 1986.
- S. V. Hung-Leo, "Computer-Aided Design of Multiple-Class Piecewise Linear Classifiers, 1983.
- F. Towfig, "Piecewise Linear Detection of Curved Edges, 1980.
- M. D. McNeil, "Digital Preprocessing of Low Contrast, Wide Dynamic Range Images," 1975.
- T. Miyatake, "Compute-Film System for Contrast Enhancement," 1972.
- D. V. Smith, "Dynamic Behavior of Time-Varying Threshold Learning Processes," 1968.

Visiting Scholars:

- Professor Minechi Kudo, Hokkaido University, Sapporo, Japan, 9 months, 1996.
- Professor Leon Bobrowski, Polish Academy of Science, Fulbright Scholar, Poland, 1 year, 1994-1995.
- Oliver Paetz, RW Technische Hochschule, Germany, 10 months, 1994-1995.
- Matthias Kroemer, RW Technische Hochschule, 6 months, 1995-1996.

Ariela Kamin, Technion -- Israel Institute of Technology, Israel 1990 -1991

Akio Shio, Nippon Telegraph and Telephone Corporation, Japan - 1.5 years 1989-1991

Professor Kalman Peleg, Technion -- Israel Institute of Technology, Israel - 5 months, 1990

Professor Peter Jensch, The University of Oldenburg, West Germany -6 weeks, 1989-1990

Ryuji Nishimura, Hitachi Ltd., Japan - 1.5 years 1989 - 1990

Dr. Thomas Tolxdorff, Rheinisch-Westfälischen Technischen Hochscule, West Germany - 4 weeks, 1989

Dr. Leon Bobrowski, Institute of Biocybernetics and Biomedical Engineering, Poland, 3 weeks, 1989

Djordije Jankovic, Boris Kidric Institute, Yugoslavia - 3 months, 1989

Professor Mirek Pawlak, The University of Manitoba, Canada - 2 months, 1989

Hideaki Doi, Hitachi Ltd, Japan - 1 year, 1988-1989

Professor Adam Krzyzak, Concordia University, Canada - 1 month, 1988.

Extramural funding since 1987:

PROGRAM TITLE	DATES	AGENCY	MONETARY LEVEL
Database-Aided Telemammography	2000-02	California Telehealth and Telemedicine Center	\$115,000
Database-Aided Diagnosis in Digital Mammography	1999-03	U. S. Army Medical Research and Materiel Command	\$1,928,000
Computer-Aided Diagnosis In Digital Mammography	1997-99	California Breast Cancer Research Program	\$214,000
Biologically Inspired Intelligent Classifiers	1992-96	NSF	\$ 330,000

Landmark Detection	1997-98	Naval Air Warfare Center	\$25,000
Line Detection and Genetic Feature Selection	1995-96	ONR	\$ 135,000
Genetic Algorithms for Target Recognition	1993-94	Naval Air Warfare Center	\$ 20,000
Digital Video for Intelligent Systems	1993-94	NSF	\$ 25,000
Target Recognition	1992-93	UC MICRO/Loral	\$ 53,000
Computer Vision	1989-92	NTT (Nippon Telegraph and Telephone Corporation)	\$ 120,000
Automated Tissue Production	1989-92	BARD (Binational Agricultural Research & Development Fund)	\$ 129,000
Neural Learning	1989-91	DARPA	\$ 300,000
Image Processing Architectures	1989-90	Rockwell/Micro	\$ 34,000
Computer Vision	1988-90	Hitachi	\$ 55,000
Automatic Pattern Classification	1987-90	Army Research Office	\$ 140,000
Discretionary Research		Hughes Aircraft	\$ 10,000

Publications:

Books:

Pattern Classifiers and Trainable Machines (with G. Wassel), Springer-Verlag, 1981

Books edited:

1. *Biomedical Images and Computers* (co-edited with J. C. Bisconte), Springer-Verlag, Heidelberg, 1982.
2. *Proceedings of the Symposium on Computer-Aided Diagnosis of Medical Images* (editor), IEEE Computer Society, November 1976.
3. *Pattern Recognition: Introduction and Foundations* (editor), Dowden, Hutchinson, and Ross, Stroudsburg, PA, 1973.

Book Chapters and Articles:

1. "Large-Scale Feature Selection" (with W. Siedlecki), *Handbook of Pattern Recognition & Computer Vision*, edited by C.H. Chen, L.F. Pau, P.S.P Wang, World Scientific, 1993, Chapter 1.3, pp. 61-123.
2. "Biomedical Image Analysis" (with P. V. Sankar and R. J. Walter), *Handbook of Pattern Recognition and Image Processing*, ed. by Young and Fu, Chapter 26, Academic Press, 1986.
3. "Two-Resolution Detection of Lung Tumors in Chest Radiographs," (with D. Petkovic), *Multiresolution Image Processing*, edited by A. Rosenfeld, Springer-Verlag, 1983, pp. 365-378.1
4. "The Use of Markov Random Fields as Models of Texture" (with Martin Hassner), *Image Modeling*, edited by A. Rosenfeld, Academic Press, 1980, pp. 185-198. Also: *Computer Graphics and Image Processing*, Vol. 12, 1980, pp. 357-370.
5. "Toward Computed Detection of Nodules in Chest Radiographs," *Real Time Medical Image Processing*: edited by M. Onoe, K. Preston, Jr., A. Rosenfeld, Plenum Press, New York, 1980, pp. 53-59.

6. "Biomedical Image Analysis," *Issues in Digital Image Processing*, edited by R. M. Haralick and J. C. Simon, published by Sijthoff and Noordhoff, Alphen, The Netherlands, 1980, pp. 291-311.
7. "Image Segmentation and Feature Extraction," *Digital Image Processing and Analysis*, edited by J. C. Simon and A. Rosenfeld, Noordhoff International Publishers, Groningen, The Netherlands, 1977.
8. "Boundary Detection in Medical Radiographs," *Digital Processing of Biomedical Images*, edited by K. Preston and M. Onoe, Plenum Press, New York, 1976, pp. 309-322.
9. "Time-Varying Threshold Learning" *Proceedings of 1966 Joint Automatic Control Conference, University of Washington*, Seattle, Washington, August, 1966, pp. 33-37. Also: *Cybernetic Problems in Bionics*, ed. by H.L. Oestreicher and D. R. More, Gordon and Breach Science Publishers, New York, 1968, pp. 687-695.

Refereed journal articles:

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51. "Digital and Cellular Convexity," (with Chul E. Kim), *Proceedings of the 1981 IEEE Computer Society Conference on Pattern Recognition and Image Processing*, pp. 156-161.
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53. "A Gestalt-guided heuristic boundary follower for x-ray images of lung nodules" (with P. V. Sankar), *Proceedings of the Thirteenth International Conference on System Sciences*, Vol. 2, January 1980, pp. 360-367.
54. "Circular-coded x-ray tomography for recording and reconstruction of three-dimensional structures" (with S. Kawata), *Proceedings of the VII International Conference Information Processing in Medical Imaging*, June 1981.
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57. "Minimal Rectangular Partitions of Digitized Blobs" (with L. Ferrari and P. V. Sankar), *Proceedings of the 5th International Conference on Pattern Recognition*, December 1980, pp. 1040-1043.
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70. "Minimal Piecewise Linear Classifiers" (with L. Michelotti), *Proceedings of Fourth International Joint Conference on Pattern Recognition*, International Association for Pattern Recognition, Kyoto, Japan, November 1978, pp. 230-232.
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72. "Target Pattern Correlation for BMD Threat Discrimination, (with Hightower, K. J. Rowe), *Proceedings of the Twenty-Third Annual Tri-Service Radar Symposium*, West Point, New York, July 13, 1977 (Classified SECRET).
73. "Medical Visual Information Processing at the University of California at Irvine," *Proceedings of the Third Annual AIM Workshop*, Rutgers University, Laboratory for Computer Science Research, New Brunswick, New Jersey 09803, July 1977, page 13.
74. "Parallel Detection of Concavities in Cellular Blobs" (with L. Cordella and S. Levialdi), *Proceedings of the Second International Joint Conference on Pattern Recognition*, Copenhagen, August 1974, pp. 143-147.
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76. "Automatic Detection of Suspicious Abnormalities in Breast Radiographs" (with H. Wechsler), *Proceedings of 1975 San Diego Biomedical Symposium*, February 1975, pp. 193-198.
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78. "Hierarchic Recognition of Tumors in Chest Radiographs" (with D. H. Ballard), *Proceedings of Second International on Pattern Recognition*, Copenhagen, August 1974, pp. 258-263.
79. "Adaptive Trackers Based on Continuous Learning Theory" (with N. J. Bershad and P. Merryman), *Proceedings of the Sixth Hawaii International Conference on System Science*, University of Hawaii, Honolulu, January, 1973.

80. "Stability of Threshold Learning," *Proceedings of the 1971 IEEE Conference on Decision and Control*, Miami Beach, Florida, December 1971.
81. "Training a One-Dimensional Classifier to Minimize the Probability of Error" (with G. Wassel), *1971 IEEE Conference on Decision and Control*, Miami Beach, Florida, December, 1971.
82. "A Parallel Mechanism for Describing Silhouettes" (with P. J. Nahin), *IEEE Trans. on Computers*, Vol. C-21, No. 11, November, 1972, pp. 1233-1239. Also: "A Parallel Mechanism for Recognizing Silhouettes," *Proceedings of IFIP Congress 71*, August 1971.
83. "Recognizing Three-Dimensional Objects by their Silhouettes" (with G. A. Davison), *Proceedings of the XXXIst Avionics Panel Technical Meeting on Artificial Intelligence*, Rome, Italy, May, 1971.
84. "A Continuous Two-Dimensional Model of Discrete One-Dimensional Threshold Learning," (with P. Merryman) *Proceedings of the 1970 IEEE Symposium on Adaptive Processes*, December, 1970.
85. A Stopping Rule for Trainable One-Dimensional Threshold Learning" (with H. R. Ramanujam) *Proceedings of the 1970 IEEE Symposium on Adaptive Processes*, December, 1970.
86. "Markov Chain Model of Adaptive Signal Detection," *1963 Bionics Symposium*, Contributed Paper Preprints, Dayton Ohio, March 20, 1963.
87. "Adaptation and Feedback," *Proceedings of the 1962 Joint Automatic Control Conference*, published by the American Institute of Electrical Engineers, 345 East 47th Street, New York, New York 10017.
88. The Application of Feedback Concepts to the Incorporation of Learning in Complex Machine Systems," *Proceedings of the Pilot Clinic on the Impact of Feedback Control Concepts on the Study of Economic and Business Systems*, New York University, October 28, 1960. Published by the Foundation for Instrumentation Education and Research, Inc., 345 East 47th Street, New York, New York.
89. "Pulsed RC Networks for Sampled-Data Systems," *IRE Convention Record, Part 2, Circuit Theory*, 1956, pp. 81-99.

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1. "An Image Storage Tube Computer," AD658521, Defense Documentation Center, Cameron, West Virginia, July, 1967.
2. "Analysis of Markov Chain Models of Adaptive Processes" (with K.R. Kaplan) Aerospace Medical Research Laboratories, Wright-Patterson Air Force Base, Ohio, Technical Report No. AMRL-TR-65-3, January, 1965.
3. Two-Mode Threshold Learning," Aerospace Medical Research Laboratories, Wright-Patterson Air Force Base, Ohio, Technical Documentary Report No. AMRL-TR0-64-39, May, 1964.
4. Network Compensation of Error-Sampled Feedback Control Systems, "Technical Report T-7/B, Electronics Research Labs., Columbia University, 632 West 125th Street, New York, 27, New York, April, 1955 (doctoral dissertation).

Popular Literature Articles:

1. "Trainable Systems," *I.E.E.E. Student Journal*, Vol. 5, No. 6, November, 1967, pp. 16-22.
2. "Adaptation Theory - A Tutorial Introduction to Current Research," *Medical Electronics and Biological Engineering*, RCA Publication PE238, RCA Laboratories, Princeton, New Jersey, 1965.

Ph. D. Dissertation: "Network Compensation of Error-Sampled Feedback Control Systems," 1955.

Public Lectures:

Radiological Society of North America, "Hot Topics" paper, 1997
UCI, Department of Electrical and Computer Engineering, 1997
King-Drew Medical Center, Invited Seminar, 1997
UCI, Department of Medicine, Seminar, 1996
UCI, Department of Radiological Sciences, Seminar, 1992
UCI, Department of ECE, Annual Review of Research 1990
University of Nebraska, EE Colloquium, Invited talk 1990
IEEE Computer Society, Orange County Chap. Invited talk 1990
Office of Naval Research Conf., St. Petersburg, Invited talk
Symposium for Computer Assisted Radiology, Anaheim, CA, Invited talk
2nd Conf. of Int. Fed. of Classification Societies, Invited lecture 1989
Technical University, Aachen, W. Germany Invited lectures, 1989
Department of Psychiatry and Human Behavior, Invited lecture 1989

Second Conference of the Intl. Fed. of Classification of Societies, Invited talk, 1989.
USC, Invited talk, 1989
Veterans Adm. Med. Center Radiology Dept. Long Beach 1989
CAR'89 Third Intl. Symposium on Computer Assisted Radiology, West Berlin, Invited lecture
UCI Dept. of Psych. and Human Behavior, Invited lecture 1988
USC Signal and Image Proceedings Institute, Invited lecture 1988
UCI Department of Radiological Sciences, Invited lecture 1988
VA Medical Center, Long Beach, CA, Invited lecture 1988
Technion, Israel Inst. of Technology, Invited lectures, 1987
GTE Government Systems Corporation, Invited lecture, 1987
George Washington University, Invited lecture, 1987
SPIE, International Soc. for Optic Engr. Invited lecture 1986.

Patents:

J. Sklansky, R. L. Thomason, "Electronic Inspection Systems and Methods of Inspection," U.S. Patent No. 4817184, March 28, 1989.

J. Sklansky, E. Vendrovsky, "Method and Apparatus for Video Data Compression," U.S. Patent No. 6008851, Dec. 28, 1999.

Patent application:

C. Ornes, J. Sklansky, "Visual Neural Classifier," U. S. Patent Application Serial No. 09/272.697, filed on March 18, 1999 by the Regents of the University of California.

Courses Taught:

Digital Signal Processing, graduate course, 1987-91

Medical Imaging Systems, graduate course, 1989-1994

Digital Signal Processing, undergraduate course, 1989-1992

Intelligent Machines, graduate course, 1966-1994

Logic and Organization of Digital Computers, undergraduate course, 1966-1988

Discrete Systems Theory, graduate course, 1975-1984

Digital Image Analysis, graduate course, 1970-1984

Computer Vision, undergraduate course, Spring 1984

Computer Architecture and Microprogramming, graduate course, 1975-1980

University Service:

- 1996-1998: Chairman of UCI Emeriti Association Welfare Committee
- 1992-1993: Chair of Department Committee to evaluate a faculty promotion to Associate Professor with tenure
- 1992-1993: Chair of Ad Hoc Senate Committee to review a faculty advancement.
- 1989-1990: Chairman of Engineering Committee to Search for Chair of Department of Electrical and Computer Engineering
- 1991-1992: Department of Electrical and Computer Engineering Committee to Search for faculty in circuits and systems
- 1991-1992: School of Engineering Executive Committee
- 1990: Ad Hoc Committee for evaluating promotion to Associate Professor with tenure.
- 1990: Ad Hoc Committee for evaluation of advance to Professor Step VI
- 1989: Member of Ad Hoc Committees for reviewing merit increases for Assistant Professors
- 1989: Chair of Ad Hoc Committee to review promotion to Associate Professor with tenure
- 1988-1989: Search Committee for senior computing faculty
- 1988-1989: Search Committee for senior systems engineering faculty
- 1988-1989: Computer Committee of School of Engineering
- 1988-1989: Senate Review Committee for Regents Lecturers and Professors
- 1988-1989: Chair of Affirmative Action for Department of Electrical Engineering
- 1988: Electrical Engineering Committee on Policy for Adjunct Professorships

- 1987: Delegate of School of Engineering to California Engineering Foundation Conference
- 1987-1988: Member of Executive Committee of Academic Senate
- 1987: Reviewer of research proposals to UC MICRO
- 1986-1988: Delegate to Academic Assembly
- 1986-1987: Chairman of Senate Ad Hoc Committee for evaluation of merit increase to Professor Step VI
- 1985-1986: Electrical Engineering Committee on Graduate Curriculum and Graduate Requirements
- 1985: UC Systemwide Committee to Review the Multicampus Institute on Transportation Studies
- 1985-1986: Engineering Committee on Procedures for Evaluation of Faculty Advancement
- 1985-1987: Chairman of Computer Engineering Faculty Search Committee
- 1985: Chairman of Electrical Engineering Planning Committee
- 1984-1987: Director of Focused Research Program on Image Engineering
- 1984: Electrical Engineering Graduate Studies Committee; editor of graduate studies brochure
- 1984: Electrical Engineering Academic Planning Committee
- 1984: Academic Planning Council of The Vice Chancellor
- 1984-1985: Chair of Senate Committee on Planning and Budget
- 1984-1985: Chair of Engineering Faculty
- 1984: ICS/Engineering Research Building Committee
- 1983: Electrical Engineering Graduate Studies Committee
- 1983: Executive Committee of Faculty of Engineering

- 1983: Senate Ad Hoc Committee to evaluate a proposed promotion to Professor
- 1982-1983: Committee for evaluating major merit increases for three senior faculty members
- 1982-1985: Graduate Committee of Department of Radiological Sciences
- 1977-1980: Advisory Cabinet for Vice Chancellor of Academic Affairs
- 1980: University-wide committee for planning the use of Governor Brown's 4-million-dollar special fund for engineering and computer science. Appointed by Academic Vice President William R. Frazer
- 1980-1982: Chairman of recruiting computer engineering faculty
- 1981: Senate Special Committee to Review the Student Recommended Faculty Program
- 1981: Senate Ad Hoc promotion committee
- 1980-1988: Faculty advisor to Chi Epsilon Mu and its successor, Tau Beta Pi, the national engineering honor society
- 1977-1978: University Coordinating Committee on Graduate Affairs
- 1977: Review of patent disclosure for UC office of the Board of Patents
- 1976: Member of Engineering Dean's Task Force for Organizational Change
- 1975-1977: Chairman of Graduate Council
- 1975: Chairman of Ad Hoc Committee for review of a faculty promotion
- 1974: Steering Committee of UCI Faculty Association
- 1974: Senate Committee on Computer Policy
- 1974: Executive Committee of Engineering Faculty
- 1974: Chairman of Graduate Council Committee to Review the Graduate Program of the School of Biological Science (the first review of a graduate program at UCI)

- 1970: Chairman of Applied Physics and Information Science group in the School of Engineering
- 1969-1970: Senate Committee on Computer Policy